DARWIN AND FREUD *

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TWICE in a century, the human self-estimate has been rudely upset by the work of one man. A hundred years ago Charles Darwin showed us that we are not unique, and before the turn of the century Sigmund Freud had shown us that we have no insight into our own motives. As a result of this double blow to tradition, thousands of people all over the world now know, or think they know, that Darwin proved that men are descended from apes, and Freud that everything is really due to sex. The geographical and social range of those misconceptions is itself a measure of the size of the revolutions: I suppose the inaccuracy is a measure of the risks one runs in correcting cherished illusions.

There are other links between the work of Darwin and Freud beside the fact that they are the godparents of man's objectivity toward Man. Darwin's *Origin of Species* had its centenary last year. It has taken the whole of that century for its implications to leaven the mass of general sciences—they are just beginning to penetrate into the most resistant fragment of all to biologically fundamental ideas, the practice of medicine. Freud's principal discoveries have been published just on half as long. They originated in medicine, as a byproduct of the search for a method of treatment. They have spread luxuriantly in the social sciences, and partly because of this luxuriance they are only just beginning to penetrate biology at all.

In fact, in putting Freud and Darwin on the same footing, I still must appease, if not convince, colleagues in all the sciences, including psychology. General scientists have treated Freud rather as the Americans have treated the Communist Chinese—by mixing a morose hostility with the public pretence that he is not there. This foreign policy—in relation to Freud at any rate—is almost certain to change, and it is important for human biology that it should.

It is not easy to put Freudian and Darwinian ideas on an equal basis of acceptability. Verification in psychoanalysis has its own special difficulties: these have lately been discussed by psychoanalysts and philosophers with a minimum of mutual comprehension (Hook 1959). The Freudians would have got further and fared better if they had talked to biologists instead; they would have found less need to resist the idea that Freud's hypotheses and methods are in some way scientifically as well as conversationally indecent.

Both Darwin's and Freud's hypotheses were developed to explain empirical observations; both are in some particulars almost certainly wrong; both have been strikingly successful in organising facts which were known but not understood when the theories appeared, and facts which have been discovered since. Both come within the ordinary scope of scientific method.

After a hundred years with a few powerfully motivated exceptions, most people now accept the main drift of Darwin's argument. After fifty years, if we take the essentials of Freud—infantile sexuality, the Œdipal reactions, dream-symbolism, defence mechanisms, and repression—some people will say, like Pasteur, " Mon Dieu, sommes-nous encore là ?"; and others will angrily deny that any of them are verifiable at all. This is probably not very different from the situation of Darwinian anthropogenesis, perhaps not fifty, but certainly twenty years after the *Origin*.

Someone has said that the best argument for Freud is that he makes intelligible sense of *Tristram Shandy*. I find that a cogent argument, and no doubt our grandfathers, if they were not morphologists, were less convinced by Darwin's vast collection of examples than by the fact that he made intelligible sense of the contents of the British Museum. In selling Freud to the general scientist, the most telling evidence may well be the goodness of fit to matters of common knowledge, rather than specialised information from clinical interviews, which is the real source of the hypotheses. Biologists know that doctors are notoriously bad exponents of scientific method: the evidence from clinical analysis, which is most impressive when one sees it, is obtained under conditions which they can neither experience easily nor control. They are right to be suspicious of it, but if clinical hypotheses can be shown to create intelligible order elsewhere, and especially in their own fields, biologists may demilitarise their offshore islands and suggest experiments to see if the hypotheses are true.

Penetration of science in this way takes time. It has to wait for new evidence, for tempers to cool, and for ineducable experts to die. We know that Darwin until recently excited, and Freud still excites, the worst possible emotions in both opponents and proponents. We know also that psychoanalysis is a special case in that we are probably dealing with matter which is uniquely able to upset our judgment. This poses a problem in scientific argument which is new, quantitatively if not qualitatively, because we have to recognise the fact of so-called " resistance ", which we can easily verify in our own experience, and which makes it as hard for some people to consider the relevant ideas is it would be for them to see into their own ears. At the same time, we have to refrain from using this as an argument on theoretical questions, because it is obviously the joker to end all rational discussion.

Let us now try and fit Darwin and Freud together and see what the speculative structure looks like.

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Darwin published the *Descent of Man* in 1871—thirteen years after the *Origin*. The whole of the evolutionary argument except the explicit application to man was really present in the earlier book. The full title of the new work was *The Descent of Man, and selection in relation to sex*. The second part of the title actually accounts for more than half the text, and deals with a matter which, though Darwin does relate it to man, is not a primary argument in his theory of human origins. It was something arising out of his general evolutionary theory which had been criticised, and this second book was an opportunity to deal with it at greater length. The

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juxtaposition of sexual selection and human descent seems therefore to have been a matter of convenience rather than relationship.

We read *The Descent* now, of course, with hindsight, and much of the argument for human evolution is familiar. In these days it is perhaps the part which dates more which we can read with greatest profit—the argument about the evolution of the higher faculties and the human sense of values. One of the privileges of our hindsight is that we can see how Darwin handles Freud's material but skirts round his interpretation of it. In his discussion of human behaviour Darwin relates the evolution of morals to family-situation, and reaches as it were the edge of the super-ego concept. But much more striking, of course, to a Freudian hindsight is the accident which sets this sort of argument side by side with the discussion of sexual dimorphism. I would not venture to suggest that Darwin was unconsciously aware of a relationship between them (if he had been, he would have been much more likely to avoid the subject altogether), but the fact remains that we now read as a unified argument something which he intended to take in two little-connected subjects.

When in the last section Darwin does apply sexual selection to Man, he puts the Freudian coping-stone on the edifice in discussing female adornment; he quotes a savage chief explaining why his womenfolk stretch their upper lips to the size of dinner-plates:

> " They are the only beautiful things women have; men have beards, women have none. What kind of person would she be without it? She would not be a woman at all, with a mouth like a man but no beard." (Darwin 1871.)

This, to the psychoanalytical reader, is like one of those film sequences in which hero and heroine tragically miss each other in opposite sides of a rotating door.

The implications of sexual dimorphism—of the fact that there are obvious anatomical differences between male and female—are critical to Freud's account of human development. In the event, Darwin tries to explain the significance of sexual dimorphism in general, but Freud explains the application of Darwin's selectionist argument to human socio-ethical behaviour, the point which Darwin was looking for but did not quite find. With this in mind we can relate the two. We shall find that not only Darwin but Freud gains in the process.

Darwin's great fundamental discovery was the idea of natural selection. It followed from this idea that any clear trend or development in form was likely to be in some way adaptive.

In some animal species, cock and hen for example, there is a striking difference between the sexes—sometimes an exorbitant one, like the clumsy, two-foot-long tail of the male quetzal, which can barely fly in mating plumage. In others, such as penguins or gulls, the sexes appear identical. Why did selection favour these differences, and in some species only? The point long worried Darwin—it underlies the remark in one of his letters that the eye no longer troubled him, but the sight of a peacock's feather made him feel sick.

His eventual explanation was two-pronged. Some of the instances represent different functions in upbringing. If men must work and women must weep, or rather suckle, one would expect this to be reflected anatomically. Others, like the peacock's tail and the stag's antlers, it was reasonable to explain as a means of competition between males by which the most vigorous would have the most progeny—either through ability to attract females and keep them attracted, or through the ability to fight rivals and monopolise the most desirable mates.

Darwin's view of sexual ornament is that in man and in animals it is chiefly competitive. But since his time interest has shifted to a related function of sexual dimorphism—its use in recognition. In territory-keeping birds, the cock drives off other cocks—often without actually fighting them—by displaying his markings and song against theirs. There are occasional violent encounters, but as a rule territories tend to subsist automatically by a form of behavioural agreement, based on the use of these signal mechanisms.

In gulls which do not have visibly different sexes, the signal is the adoption of a particular posture (Tinbergen and Moynihan 1952). The cock bird defending his territory takes up a threat posture—if the intruder is also a cock, he will retaliate or retreat, but a hen will carry out an appeasement display, taking up a posture as different as possible from the threat position.

This meets the need to distinguish a potential, or an accepted, mate or mates from an intruder. The other tolerated parties on a territory are the young. These are usually protected from being driven away prematurely by the fact that the behaviour or markings which trigger the aggressive response of the parents do not appear until sexual maturity. This is necessary in species where parental dependence goes on until the young are as big as the adults. In other species, there are precautions to keep the young away from an aggressive parent. Though brown bears are commonly monogamous, cubs never see their father, and are not deserted by the mother until they are big enough to climb out of his reach (Couturier 1954). Young male Northern fur seal (Scheffer and Wilke 1953) live with the cows until shortly after spermatogenesis begins, when they go off alone and do not return until they have rapidly grown enough muscle to take place in the dominance-order of males. In general, a long-term family-situation in pair-mating animals has two requirements—that other sexually active individuals should be driven away, either from a territory or from the female, and that the young and the accepted mate should not.

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Freud had little Darwinian background. His only obvious debt to Darwin is the idea of a primal horde in which the strongest male ruled. But it was an important debt, because it started him with a firmly Darwinian idea that sexual dimorphism was primarily competitive. He did not, however, really apply the selectionist argument to his central and most surprising finding—the nature of the anxiety behind the human fear of incest, an anxiety which seems in many ways to have dominated human social development, the so-called castration fear. This was an empirical observation which he had great difficulty in explaining—and, as Darwin had to invent the idea of pangenesis because he had not seen the work of Mendel, so Freud was obliged to turn to racial memory to account for something which makes sense in evolutionary terms but in virtually no others.

Freud found that in his patients' conscious behaviour, normal and abnormal, was influenced by thought-patterns which were unconscious and followed characteristic non-rational sequences. Much of their content was sexual, and seemed to date from early childhood, and there was an extremely powerful block to making conscious its original significance.

The imagery showed an extraordinary preoccupation with the external genitalia, with fantasies of incest. and with fantasies of castration. This system of unconscious imagery and associated anxieties Freud called the Œdipus complex—after the Greek hero who inadvertently killed his father, married his mother, and blinded—or castrated—himself in expiation. It appeared to date from a particular period in childhood, between the ages of four and six, and the associations behind it were remarkably consistent, one of the chief components being intense anxiety over the difference between the sexes, combined, in the male child, with a fear of injury to his own

genitalia. The female organs were a particular focus of this anxiety. They seemed to be interpreted as a wound or mutilation which was in itself threatening. The male child apparently saw them as threat of castration, while the female child came to think of herself as actually deprived of a male organ.

Freud was as impressed as we are by the oddity of this at first sight, but once he had recognised the irrational train of thought behind it, it became obvious that there were echoes of it all over human behaviour, custom, and literature, which become progressively more striking as we get used to the peculiar kind of non-conceptual association which determines unconscious imagery. The outburst of anxiety appeared to be connected with another mechanism which Freud had been obliged to postulate—the sexual attraction of the male child to its mother, and its resentment toward, and fear of reprisals from, the father.

Given the existence of infantile sexuality, which was perhaps the most biologically surprising part of the story, it seemed reasonable that the sexual object for a male child should be the mother, and that the father should be felt as a rival. But where did the fear of castration come from? It was important, because it seemed to be the driving-force behind the peculiar human incest-anxiety and behind the adult behaviour-disorders Freud was investigating.

Freud at first attributed it to injudicious threats from parents, and wondered whether he might not himself be suggesting it inadvertently to adults during treatment. But it became clear that where there had been threats these only aggravated a fear already present, which seemed to appear spontaneously at the appropriate age.

It was found in children who had never been threatened, children who had no parents, and in places where the psychoanalyst could not possibly have put it, from Greek mythology to *Tristram Shandy*—in the impolite ballad, for example, which gave us the phrase "pull Devil, pull baker" and which repeats the typical concerns verbatim, even down to the interpretation of the vulva as a castrating wound (Farmer 1897), turning them to reassuring mockery.

There are two obvious biological comments at this point. Both have already been made by a psychoanalyst (Fenichel 1954). The first is that the Œdipal responses not only have every appearance of being in some way built in, but that they look uncommonly like a temporary organ with a function. The second is that sexuality, in its biological as well as its conversational sense, is a correlate of reproduction. The mention of infantile sexuality at once calls for some explanation of what sexuality is doing in infancy. Some infant animals show minor sexual reflexes, such as erectility, but well-developed sexual drives in infancy would be an example of what is called anticipation, and this kind of shift makes one look for a possible adaptation of an old mechanism to a new function.

Freud did in fact recognise the Œdipal reactions as being built in. The tendency of his time would have been to label them instinctive, but this Freud would not do. Not, curiously enough, because of the extreme difficulty of justifying alleged human instincts, and the uncertainty how much any built-in response owes to shared experience, but because he had throughout life a fixed idea that there could be two human instincts and two only—the two posts were held by different candidates at different points in his career, but at that time both were occupied. Instead he turned to the idea of racial memory. The castration fear and the associated anxieties were inappropriate to the childhood situation in any known human society, but they might not always have been. They could be intimations of fiercer sexual selection in the primal horde, where the sons had to kill their father to possess his wives, but having rudimentary ethical qualms, as Darwin said they must, they had bequeathed anxiety to their descendants. We find him wondering if there were ever a time when the father really castrated his sons, or whether the threat was enough (Jones 1955).

If human sexuality had in fact been brought forward into pre-reproductive life, and had acquired a new place in behavioural development, the Œdipal reactions with their peculiar genital content could be part of this shift, or the result of it. We might reasonably look to see if there is any other peculiarity of human development which makes anticipation likely. In fact there is. The curve of human growth and development differs conspicuously from that of non-primates, such as the sheep, in having a long lag-period inserted between the fifth and the ninth years.

The development which in other mammals is continuous is divided in man into two: an early phase, which is isolated from sexual maturity by the whole length of childhood, and a pre-reproductive phase which coincides with the beginning of puberty and the appearance of secondary sex characters. The two peaks of psychosexual development in Freud's timetable therefore fit accurately over two periods of maximum growth and developmental rate, which were presumably once continuous but are now separated by the lag—and by the Freudian latency period (Hutchinson 1930).

Castration anxiety, which has every appearance of fulfilling a special function, but which seems inappropriate to childhood in any known human society, would be much less so in an animal which had no lag-period, and in which it could represent an adaptation which protected immature males over the awkward age between sexing and achieving competitive size. (Lampl 1953, Szekely 1957). If there was no lag period in man, puberty would be complete about the age of 9. The timing of the Œdipal reactions (4–6 years) would therefore still put them well ahead of the probable age of appearance of secondary sex characters; more recent workers have put them if anything earlier still. But Freudian experience has always insisted that the onset of castration anxiety is in some way triggered by the recognition of the genitalia themselves. This is possibly an important clue to its origins.

The timing and content of the reaction in man would be intelligible if it evolved originally (*a*) among pair-mating animals; (*b*) with prolonged and lengthening maternal dependence; (*c*) if instead of the secondary sex characters, the genitalia themselves were rather suddenly to become the primary sex signals, so that males became competitive long before they were mature. This might happen as a by-product of unconnected changes—e.g., posture or hair density—or even by an interference between growing intelligence (which learned to associate male genitalia with male secondary sex characters) and instinct (which excited hostility to them). It would call for a major adaptation in behaviour to maintain the family-pattern. If young males must love their mother in order to stay at home, but not approach her in a manner which led to their being driven away, avoidance of the sexually displaying female as a castration threat, and mixed feelings towards the adult male, in which his genitalia served as a dominance-signal, could serve to keep them out of the competitive situation while still maternally dependent.

An explanation of this kind can be manipulated to include most of the peculiarities of human psychosexual imagery, including its remarkable concentration on phallic and vulvar symbolism to the exclusion of other

sex characters—even down to details like the tendency to interpret the father's penis as a castrating object. It also seems to chime with the importance which some writers have attached to the primal scene.

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Perhaps the oddest biological feature of human psychosexual development is its surprising and un-Darwinian vagueness of aim. Fixity of sexual object, at least to the extent of mating with a potentially fertile female, would seem to be the behavioural minimum to be expected in a system where "fitness" is a correlate, simply, of total fertile progeny; the nadir of unfitness is inability or unwillingness to breed. But the human sexual object is not fixed—under present conditions at least, it is rather easily displaced. Almost all such displacements reduce their possessor's reproductive effectiveness, and many prevent mating altogether. According to Freud, the liability to these deviations is a direct hazard of the Œdipal processes, and of the need, effectively, to reverse or overcome the avoidance of the female before adult reproduction becomes possible. Persistence of this anxiety may divert the sexual drive away from its proper target and dissipate it on an irrelevant one—a member of the same sex, an inappropriate part of the body, or an inanimate object.

There is more, in all probability, to the biology of paraphilias than this—one was recently excised surgically, along with a temporal lobe epileptogenic focus (Mitchell et al. 1954)—but they set essentially the same evolutionary problem whatever their cause. The human pattern of development carries, empirically, a sizeable risk of interference with eventual mating. There is a strong temptation to apply here what Haldane once called Pangloss' theorem. Both Freud and Dr. Pangloss might have joined in Sinibaldi's (1642) disputation; "An potuisset natura commodius alibi viri genitale collocare; et cur unum tantum, non duo, ediderit?". According to Pangloss, if everything is for the best in the best of selectionist worlds, the peculiar mode of human sexual development must involve some overriding gain to the species; if not, it would have disappeared, or at least become reliable. This is a fallacy. Natural selection responds; it does not plan, though when equilibria shift it will compensate. The psychosexual pattern in man looks very much like the end-product of a biological emergency. The castration-fear is not, for example, sex-limited; instead, it is developed in the female into a rather cumbersome mechanism of "cryptandric" behaviour by which the male is helped, as it were, in reversing his responses and reaching the adult pattern. The non-teleological untidiness of this seems typical of the evolutionary "demon" making do. At the same time there is this much validity in the Panglossian argument; where a homoeostatic swing of this kind opens a new possibility, selection may exploit and expand it.

The Œdipal responses may carry an inherent risk of interference with eventual reproduction, but their persistence suggests a new adaptive function in their new situation. It seems reasonable to suggest that this function is morphogenetic, and that they have been positively selected because of their effects on human mental and social development. It is not impossible that by necessitating repression and a mind divided actively into conscious and unconscious levels they produced the most significant adaptation in mammalian history, the emergence of conceptual thought.

There is another aspect of this question (which is a special case of Darwin's sexual selection) quite independent of the correctness of Freud's view that miscarriages in the Œdipal stage cause paraphilias—and even of Freud's psychology generally. It is, of course, an old notion that paraphilia may be constitutional.

Kallmann (1952) found that identical twins are more like in this, as in every other, investigated respect than are fraternal twins. This means little, but there may, and some would say there must, be some "constitutional" factors behind such behaviour disorders, at least within a given culture pattern. Consideration of this in Darwin's terms has led Hutchinson (1959) to make an important suggestion—the first I have mentioned here which is directly open to experiment. If any hereditary factor regularly predisposed to paraphilia severe enough to block reproduction, there should be heavy selection against it. Hutchinson has attempted to guess what kind of physical trait might have this effect, and asks whether constitutional differences between normal and abnormal psychosexual development may not depend on individual differences of developmental rate.

There are in fact, as we have seen, strong phylogenetic reasons for associating rate-determining mechanisms with the way in which human sexuality has evolved—it arises, apparently, from allometry in the early scale of growth time. Some of the most critical processes apparently fall at a point in the growth curve where, owing to its shape, a small change in contributing rates might produce a very large change in the duration of a "temporary organ", by moving it, like the bubble in the spirit-level, along the entire extent of the "plateau" (Comfort 1959). A difference of rate, heritable or otherwise, which displaced the Œdipal behaviour by six months in an animal whose curve was continuous might shift it in man by several years, and make it persist throughout the whole of the lag-phase—during which, presumably, attitudes and behavioural patterns are hardening.

In making his suggestion Hutchinson is primarily concerned with the reasons which might prevent constitutional determinants of paraphilias from being eliminated by selection. They might follow Penrose's model for the inheritance of intelligence; that is, they might, especially if they operate primarily through rate-differences, represent multiple homozygotes of genes which persist in the population through the greater fitness of their heterozygotes (Penrose 1955).

Apart from the fact that the real importance of constitutional factors in paraphilias has yet to be established, I prefer to heed Professor Medawar's warnings about this argument and about genetical speculation generally (Medawar 1960). The Panglossian, of course, will forge right ahead. If overdominance will not do, Darwin's concept of indirect selection is ready to hand. Both intelligence and neurosis are possible factors in social development: perhaps the need for repression enlarged the brain—perhaps as I have hinted, it gave us a differentiated ego and therefore conceptual thought. Or did the prehuman community benefit from its unusually-motivated members, and from the sublimatory expression of their drives? After all, Freud suggests that the Œdipal reactions have behavioural effects far wider than the production of paraphilias. Darwin and Freud, like the rest of us, owe their unusual insights partly to their psychosexual histories. Man, Pangloss would say, when we can catch him, may owe his reason to repression and his present existence to the advice which aim-inhibited palæolithic geniuses gave to their normal but uninspired colleagues.

You may remember Belloc's theory of the spots and teeth of the microbe:

> All this has never yet been seen—
> But Scientists who ought to know
> Assure us that it Must Be So:
> O, Let us never, never doubt
> What nobody is Sure About!

These Panglossian ideas are, in other words, even more unprofitably speculative than the others I have been assessing. Hutchinson's suggestion about developmental rates, by contrast, is in principle verifiable, though prob-

ably not from existing data, and it comes at a time when we are becoming aware from the work of Tanner (1955) and others, of the large range of variation in normal human growth and developmental patterns at puberty.

In fact, the single piece of relevant evidence about a relation between timing and mental health is negative—in children with constitutional precocious puberty, whose growth curve is continuous like that in sheep (Jolly 1955), and who have no lag-period, physical puberty is complete at 6–8 years, but there is said to be no parallel acceleration in mental, libidinal, or—oddly enough—dental development (Money and Hampson 1955).

Environmental effects on psychosexual development are usually discussed in terms of traumatic experience, with much less attention to the additional possibility of direct physical retardation. Greenacre (1953, 1955) found that the early traumatic experience in paraphilics was often an illness between the second and fourth year. Illness and separation from parents may indeed be psychical stresses, but, particularly in children, where emotion itself affects appetite, they produce physical checking as well. The effects of such checks to growth in size in young humans and animals are usually made good by the "post-inhibitory growth rebound", but this may not restore complete isometry, or deal with any discrepancies which have arisen in psychical development. It is an idea worth examining.

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Nobody would deny, I think, that since Freud psychoanalytic theory has sometimes become etiolated through lack of contact with general biology, while general biology has never come to terms with the far-reaching consequences of psychoanalysis, even by recognising the way in which unconscious motives can affect observation and reasoning. One of the difficulties is that in this country there seem to be too few common-rooms in which working biologists and working psychoanalysts can come into daily contact, or even collision. This is something we should remedy. The marriage of psychoanalysis and biology is long overdue and likely to be fertile, for each has a great deal to teach the other. If between us we were able to ensure the full development of all adults, in a world which seems to call increasingly for adult minds, rather than aggregates of reaction-formations, we should certainly effect a change in human affairs which would be truly evolutionary in Darwin's sense, and justify his confidence in human reason. We might then find it a sobering experience to see how much of our present personal, social, religious, political, and scientific behaviour had been shaped in the past by mechanisms evolved (the man in the street will by then be telling us) to stop ancient monkeys from fighting their parents.

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EXPANDING THE INDICATIONS FOR TREATMENT WITH THE ARTIFICIAL KIDNEY

BURNS, CEREBRAL ŒDEMA, SULPHONAMIDE INTOXICATION, AND CONGESTIVE HEART-FAILURE

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MORE than 180 centres using artificial kidneys with disposable dialysing units are established in hospitals in the United States and many are being established throughout the world.

Artificial kidneys were first developed (Kolff and Berk 1944) to relieve the distressing symptoms (Kolff 1947) of renal failure. The purpose of dialysis with the artificial kidney is to remove retention products and to correct abnormal electrolyte concentrations. At the same time, by electively increasing the perfusion pressure in the dialysing system by a screw clamp on the outflow tract, it is possible to remove varying quantities of fluid by ultrafiltration.

The lifesaving result of dialysis in acute renal failure has been widely recorded. In chronic renal failure artificial kidneys can alleviate the symptoms of uræmia and sometimes induce gratifying clinical remissions (Goldner et al. 1954). The application of hæmodialysis to various types of poisoning, such as that caused by barbiturates, salicylates, bromides, and other substances, is well established (Kolff 1954, Schreiner 1958). It is, however, little realised that the advent of ultrafiltration to remove œdema—especially pulmonary œdema—has greatly expanded the clinical usefulness of artificial kidneys (Kolff and Leonards 1954, Kelemen and Kolff 1959). Regional heparinisation has virtually eliminated the danger of hæmorrhage during dialysis (Anderson and Kolff 1959). The artificial kidney may also be helpful when certain medical and surgical conditions *other* than uræmia, as customarily defined in biochemical terms, are the preponderant problems. We report here a series of cases illustrating these wider indications for dialysis and ultrafiltration.

Methods

The intake of fluids was restricted to 600 ml. in 24 hours when the patient was anuric (Kolff 1955a). Electrolytes were not administered unless they were demonstrably lost (Kolff 1955b). A forced high-caloric, low-protein diet was instituted as far as was practical (Kolff 1952). Twin-coil artificial kidneys were used, with the technique previously described (Kolff and Watschinger 1956, Aoyama and Kolff 1957). In adults dialysis usually lasted 6 hours. The radial artery or long saphenous vein was used to draw blood from the patient; any other vein to return it. When hæmorrhage was expected, regional heparinisation (Anderson and Kolff 1959) was used to

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reduce or to eliminate the systemic effect of the heparin: while heparin was administered by constant drip under pressure to the blood-inflow tube to the artificial kidney, protamine sulphate was simultaneously administered to the outflow tube.

Case-reports

THE FIRST CASE

Burns Causing Prerenal Uræmia (fig. 1)

A man aged 72 sustained burns of second and third degree of his trunk and limbs, involving about 30% of his body surface, when a power lawn-mower exploded. He was given the customary therapy at his local hospital, but he became drowsy and was transferred to Cleveland Clinic Hospital for consideration of treatment with the artificial kidney.

On admission, 6 days after the accident, he was semi-comatose but could be roused. He showed Kussmaul's respiration, and œdema of the lung bases and of the lower half of his body. On the 7th day he could no longer talk; his breathing was deeper and more laboured, bronchial secretions had begun to accumulate, and bronchopneumonia seemed imminent. The concentrations of serum electrolytes were within the normal range, but the carbon-dioxide combining-power of the plasma was 17·6 mEq. per litre and the blood-urea level was 231 mg. per 100 ml., although he was passing more than a litre of urine daily with a urea concentration of 2 g. per 100 ml.

In view of his rapid clinical deterioration, a dialysis lasting $5^1/_2$ hours was performed on the 8th day. Marked improvement followed, exemplified by his clinical state, reduction of the blood-urea level and increase of the carbon-dioxide combining-power. On the 10th day, dialysis had to be repeated, because the patient's renal function was not adequate to maintain the improvement. During dialysis ultrafiltration was employed to remove excess fluid. On the following days the urinary output rose to more than 2 litres per day, and this sufficed to maintain him in equilibrium and free from symptoms of uræmia, although the blood-urea level remained elevated. The usual surgical and nutritional regimen for severe burns then led to full recovery.

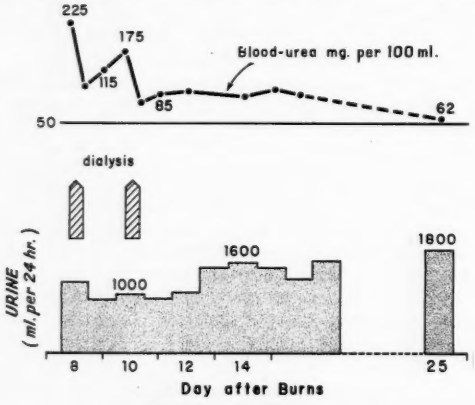

Fig. 1 (case 1)—Burns.

This case illustrates the occurrence of clinical uræmia in the presence of an output of more than 1 litre of urine of good concentration. The uræmia was due to a combination of marked hypercatabolism and slightly diminished renal function. This patient would undoubtedly have succumbed to pulmonary œdema, bronchopneumonia, and uræmia had not two dialyses with ultrafiltration removed the œdema and restored consciousness, thus enabling him to cooperate in the physical therapy for his pulmonary infection.

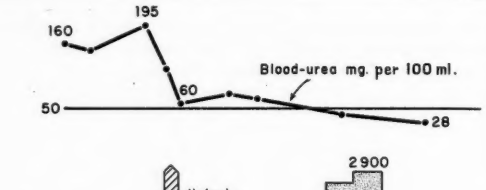

Fig. 2 (case 2)—Leptospirosis.

THE SECOND CASE

Leptospiral Nephritis (fig. 2)

A man, aged 28, a worker in an abattoir, suddenly became ill and next day had a high fever with headache, blurring of vision, and vomiting. There was no history of a preceding sore throat. He remained febrile and on the 4th day became oliguric; hæmaturia developed on the 5th day.

On admission on the 7th day he was found to be tall, muscular, febrile, and delirious. Although not showing pitting œdema, he was overhydrated. There was much muscular tenderness and conjunctival injection. No other abnormalities were found except slight bilateral renal tenderness and a solitary retinal hæmorrhage. The blood-pressure was 140/80 mm. Hg. Urinalysis disclosed albumin, red and white cells, and casts. The blood-urea level was 160 mg. per 100 ml. The urinary output averaged 1350 ml. per day on the 7th, 8th, and 9th days. The mental disturbance was out of proportion to the degree of manifest biochemical derangement. He was restless and disoriented, and, being very strong, became destructive to the point of tearing the curtains.

Hoping to improve his mental disturbance, we treated him, on the 12th day, with a 6-hour dialysis with ultrafiltration. Anæsthesia with intravenous pentobarbitone sodium was required to permit cannulation of the blood-vessels. Regional heparinisation was used to avoid an increase of hæmaturia. Next morning the patient was still pyrexial but his delirium had gone. He said that he felt well and he had little recollection of the events of the previous few days. His further progress proved uneventful, and on discharge, 11 days after dialysis, his blood-urea level had returned to normal and his urine was free of albumin and casts. In 15 days he had lost 15 lb. in weight. A tentative diagnosis of leptospirosis was confirmed after his discharge by a titre which rose from 1/64 to 1/1024 in an agglutination-lysis test against *Leptospira pomona*.

This patient would probably have recovered without dialysis; however, the nursing and nutritional problems of treating a strong, confused patient were considerably eased by his return to mental normality within 12 hours of the dialysis and ultrafiltration. We think it unsafe to allow a patient to remain in a state of uræmia and electrolyte and water imbalance when this is evidently causing severe symptoms. The condition may get out of hand and permanent brain damage may ensue. Since it is now well recognised that brain damage can result from hypoxic, hypotensive, ischæmic, and hypoglycæmic episodes, there is reason to believe that uræmia and other chemical imbalances may lead to similar damage.

THE THIRD CASE

Anuria due to Sulphadiazine (fig. 3)

Meningitis developed in a woman of 46 a week after a laminectomy for severe sciatica. Therapy was commenced

with chloramphenicol, 250 mg. every 6 hours, and sulphadiazine, 7·5 g., given fairly rapidly intravenously in 1000 ml. of 5% dextrose solution. In addition a total of 7 g. of sulphadiazine was given by mouth during the first 3 days. At the end of the 3rd day gross hæmaturia and oliguria developed. The blood-sulphadiazine was found to be 39 mg. per 100 ml. At cystoscopy crystals of conjugated sulphadiazine were seen protruding from both ureteric orifices. Both ureters were irrigated with warm saline solution, and the ureteral catheters were left in place. In spite of the free return of irrigation fluid from the renal pelves, no urine was produced during the next 36 hours. At this time the blood-sulphadiazine level was still 35 mg. per 100 ml. and it was believed that either mechanical blockage or other damage was present proximal to the renal pelves. It was therefore decided to dialyse this patient to remove the accumulated sulphadiazine as well as the excess fluid which had accumulated from intravenous therapy and metabolic oxidative processes.

The blood-sulphadiazine levels before and after dialysis were 26 mg. per 100 ml. and 11 mg. respectively. During the dialysis 180 ml. of heavily bloodstained urine was obtained from the left kidney. Next day the urinary output was 250 ml. and it rose to exceed 2 litres per day by the 6th day after dialysis. Some impairment of renal concentration mechanisms was evidenced by a urinary urea concentration of 360 mg. per 100 ml. with a blood-urea level of 77 mg. per 100 ml. on the 4th postdialysis day. 12 days after dialysis the urinary urea

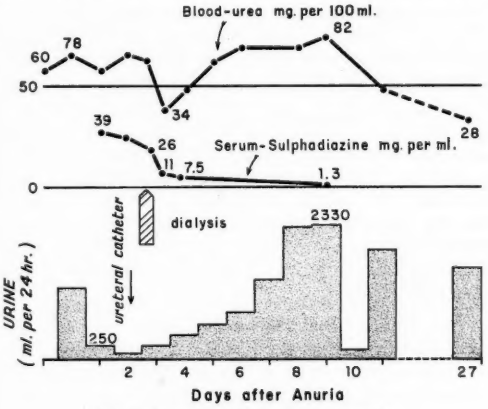

Fig. 3 (case 3)—Sulphadiazine anuria.

concentration had risen to 620 mg. with a blood-urea level of 39 mg. The patient recovered.

The fact that renal concentrating-powers may remain impaired for a period after anuria caused by sulphadiazine confirms the belief that the anuria is sometimes not due to the effects of urinary tract obstruction alone but that tubular function can also be affected. There is a twofold purpose in dialysing a patient with sulphadiazine anuria: (1) to reduce the body content of sulphadiazine (as reflected in the serum levels); and (2) to correct the metabolic disturbances resulting from anuria.

THE FOURTH CASE

Resistant Congestive Heart-failure

A man of 52 had a long history of angina and had sustained a myocardial infarction a year previously. For 2 years he had been orthopnœic in spite of a regular cardiac regimen with digitalis therapy. In the week preceding admission he had received a daily mercurial diuretic.

On admission he was in severe congestive cardiac failure and was extremely cyanotic. The blood-pressure was 102/70 mm. Hg. There was sinus rhythm, gross cardiac enlargement, and prediastolic and protodiastolic gallop. Many crepitations

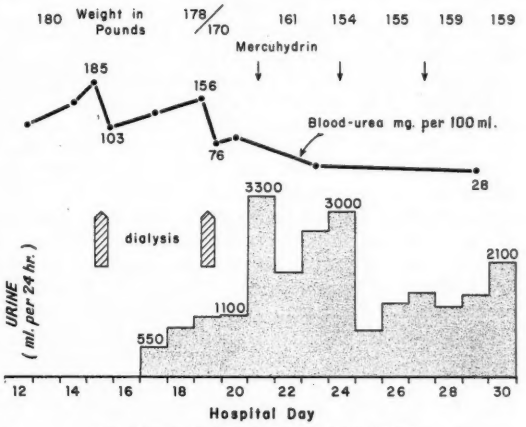

Fig. 4 (case 4)—Congestive cardiac failure.

were heard over the lung bases, and overlying pleural effusions were evident. The edge of the liver was felt four finger-breadths below the costal margin, and there was slight sacral and tibial œdema. The electrocardiogram was in keeping with an old anterior myocardial infarction, and radiography of the chest confirmed cardiac enlargement and pulmonary œdema. The urine contained a trace of albumin, a few hyaline casts, and white cells. There was a moderate iron-deficiency anæmia. Initial determinations of serum-electrolyte and carbon-dioxide concentrations were within normal limits, and the blood-urea level was 50 mg. per 100 ml. He was kept in bed, on a daily intake of 1200 calories with 500 mg. of sodium, and full doses of digitalis and parenteral mercurial diuretics were given.

On this regimen the patient lost 20 lb. in weight in 10 days but his clinical status remained unchanged. During the next 5 days he became oliguric and his weight increased. On his 15th day in the hospital he had an epileptiform convulsion. At that time laboratory studies disclosed: severe acidosis with a carbon-dioxide combining-power of 9 mEq. per litre, serum-sodium content 122 mEq. per litre, serum-potassium content 5 mEq. per litre, and blood-urea level 185 mg. per 100 ml.

It was hoped that a dialysis and ultrafiltration might rid him of several litres of excess body fluid and might also make him responsive to the action of diuretics again. Both of these hopes were realised. On the 15th day a 6-hour dialysis was performed under a filtration pressure of 280 mm. Hg measured in the outflow tract of the artificial kidney. During the dialysis he became less drowsy but no great clinical benefit was observed in spite of biochemical improvement and a rise in the carbon-dioxide combining-power from 8·2 to 15·9 mEq. per litre. A second dialysis plus ultrafiltration was done on the 19th day, during which the patient lost 4 kg. in weight, indicating that 4 litres of fluid had been removed. A renewed trial of the mercurial diuretics used previously without success now resulted in a diuresis of more than 3 litres in 24 hours. Progress after this was uninterrupted. The patient was discharged 12 days after the second dialysis with a blood-urea level of 28 mg. per 100 ml. He was free from œdema and had no signs of cardiac failure.

While dialysis corrected electrolyte concentrations and acid-base disturbances and removed retention products, ultrafiltration reduced overhydration. This changed the patient's entire internal environment, making him responsive to diuretic drugs to which he had been refractory. It is unlikely that the intravenous administration of saline solution to such an ill subject before the dialysis would have resulted in anything other than further fluid retention and deterioration.

Discussion

The use of the *rotating-drum* type of artificial kidney for patients with potentially reversible renal failure has been discussed recently by Parsons and McCracken (1959) in England. This machine is efficient in removing urea and other retention products and in correcting electrolyte disturbances. The introduction of a disposable *twin-coil dialysing unit* (Kolff and Watschinger 1956) has simplified the preparation and shortened the time required before dialysis can proceed. The dead space of the machine, once it is in operation, is fairly constant at 1100 ml., so that the patient does not experience sudden hypovolæmia or hypervolemia. Leakage of the coil has been practically eliminated. However, the main advantage of the disposable twin-coil type of dialysing unit lies in the facility with which it permits electively the removal of excess body fluid. By increasing the pressure in the dialysing coil with an adjustable screw clamp on the outflow tract to a maximum of 300 mm. Hg, as much as 1200 ml. per hour of excess fluid may be removed by ultrafiltration (Black 1959, Holmes and Nakamoto 1959). The resulting reduction of pulmonary œdema during the first $1^1/_2$ hours of dialysis and ultrafiltration can be dramatic. It is thus occasionally possible to break the vicious circle of progressive congestive cardiac failure with its attendant disturbances of renal function by a careful and well-timed dialysis with ultrafiltration.

Summary

The disposable twin-coil type of artificial kidney removes retention products (including metabolic acids), normalises the electrolyte composition of the extracellular fluid, and removes excess fluid by ultrafiltration. Regional heparinisation removes the danger of hæmorrhage.

Four patients had renal failure and some degree of uræmia, but there were other factors that provided the main indication for treatment with the artificial kidney:

(1) A 72-year-old man with extensive burns was too soporose to expectorate, was on the margin of coma, and bronchopneumonia was likely to develop.

(2) A 28-year-old man with nephritis caused by *Leptospira pomona* was too irrational and delirious to be managed. This was thought to be on the basis of cerebral œdema, and the patient became mentally normal after dialysis with ultrafiltration.

(3) A 46-year-old woman had sulphadiazine intoxication and anuria which persisted after catheterisation of both ureters. The sulphadiazine level of the blood before dialysis was 35 mg. per 100 ml.

(4) A 52-year-old man had congestive heart-failure which resisted therapy. After two dialyses plus ultrafiltration he became responsive to mercurial diuretics.

All four patients recovered.

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OBSERVATIONS ON DEHYDRATION AND SWEATING

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WHETHER or not the sweat-rate of a man exposed to environmental heat is reduced by restricting the amount of fluid he drinks has been a vexed question. Experimental results have been contradictory, but the weight of the evidence led Adolph (1947), Robinson (1949), and Bass and Henschel (1956) to conclude that sweating responds to the requirements of body-temperature regulation and is not reduced in amount by the development of dehydration. Within the past few years, however, earlier dissenters (Pitts et al. 1944, Ellis et al. 1954) have been supported by an increasing amount of evidence that thermal sweating is reduced by dehydration, and progressively so. Some of this information comes from the laboratories of Robinson (Pearcy et al. 1956, Robinson et al. 1956) and of Bass (Buskirk et al. 1958) and suggests a change in the opinions previously expressed by these experienced workers.

The obvious implication is that inadequate sweating might result in thermo-regulatory failure in men who do not drink enough while living and working in high temperatures. Recently, Bannister (1959), describing 12 cases of failure of sweating in British troops in Aden, discounted dehydration as a possible cause although he thought that most of his patients had moderate water-depletion.

In this paper we report an incidental finding of voluntary dehydration and reduced sweat-rates during studies of acclimatisation of British troops stationed in Bahrein in the summer of 1959.

Methods

18 young fit men of the Royal Air Force were studied before and after their transfer from the United Kingdom to Bahrein.

Before leaving this country, they were the subjects of several investigations carried out on our behalf by R.A.F. medical officers at the various stations in England and Scotland from which the men were drawn. These investigations included measurement daily for three consecutive days, of nude body-weights, recumbent (for ten minutes) pulse-rates and blood-pressures, and immediate erect pulse-rates and blood-pressures, also of the volumes and specific gravities of twenty-four-hour specimens of urine.

The subjects arrived in Bahrein in two groups of 10 and 8 men on June 28 and July 20 respectively, and for neither group had the journey by air occupied more than sixteen hours. According to local practice, they took up routine duties on their second full day in Bahrein, and came at the same time under our daily observation. They were almost all mechanics or fitters or wireless operators, so their duties were mainly skilled and manipulative in character. Their work and their use of leisure hours were virtually uninfluenced by their being the subjects of an investigation, and they received from us no formal instruction or advice about how much food, water, and salt they were to take.

The investigations which had been carried out in the United Kingdom were repeated in Bahrein, this time twice daily for ten consecutive days. The subjects followed daily the same routine. They began work at 7.30 a.m., and between 9.00 and 10.30 A.M. and again two hours later they came in turn to the laboratory where the observations were made. They spent

about fifteen minutes at the laboratory on each occasion and went back to work in the two hours between visits. They handed in daily the urine specimens they had collected in the previous twenty-four hours.

Systolic and diastolic blood-pressures, in both recumbent and erect positions, were measured on a sphygmomanometer by the auscultatory method. Blood-pressure measurements were made in Bahrein on only one of the two groups of subjects. Recumbent pulse-rates were counted over a full minute after ten minutes' rest, whereas erect pulse-rates were counted over fifteen seconds immediately after the subjects stood up. A balance sensitive to within 5 g. was used for the measurement of nude body-weights and careful note was made of the time of each weighing. The reductions in weights observed daily at the second weighings were taken to represent the subjects' sweat losses in the two hours or so between weighings, after corrections for fluid intake or output. In fact, such corrections were seldom necessary because the subjects were anxious to cooperate and mostly refrained from eating or drinking and from passing urine or faeces between weighings. The sweat losses observed were in each case converted to losses per hour and expressed as g. per kg. per hour—i.e., as the weight lost per man in grammes per kilogramme of his initial or "starting" body-weight. Although we have expressed the weight losses in terms of sweat rates, an indefinable but relatively small proportion of each was due to the insensible loss of water from lungs and skin.

Environmental conditions of temperature, humidity, and air-movement were measured during duty hours in the principal places where the subjects worked. They worked usually in the shade and sometimes in the sun; but for all except the wireless operators who worked in an air-cooled room, the environmental conditions were much the same and were essentially similar to those encountered out of doors, in the shade. Air temperatures and humidities were measured by a sling hygrometer with dry-bulb (D.B.) and wet-bulb (W.B.) thermometers. The method is described by Bedford (1946).

For the first group of subjects, studied in early July, sling-hygrometer temperatures at 11.00 A.M. each day were D.B. 93°F (91–94°) and W.B. 79°F (76–81°); and for the second group, in late July, the corresponding figures were D.B. 94°F (93–95°) and W.B. 81°F (77–83°). In each case these temperatures imposed a heat load much greater than that to which the subjects were exposed before leaving this country.

Results

The average amount of urine passed in twenty-four hours by the subjects before they left the United Kingdom was 1070 ml., whereas in Bahrein the average of 168 such specimens was 567 ml. We were impressed by the very small amounts of urine passed in Bahrein, for 48% of the twenty-four-hour specimens collected there were below 500 ml. and 10% were 300 ml. or less. Such small volumes of urine have not been a feature of previous studies we have made of acclimatisation in the Persian Gulf area; for example, young men entering for the first time the heat of Kuwait in 1957 and 1958 were able to maintain an average output of 1400 ml. (unpublished observations).

The small samples collected by our subjects in Bahrein were assumed to represent their entire twenty-four-hour outputs, and the expected relation between urine volume and specific gravity was observed. In most of the samples which were smaller than 500 ml., the specific gravities were above 1030. There seemed to be no doubt that the men were drinking too little fluid and were probably often in a state of water debt.

This view was not contradicted by their apparent wellbeing or by the ease with which they carried out their predominantly light duties. There was in fact some evidence that their acclimatisation (which will be discussed elsewhere) was modified by their inadequate intakes of fluid. Increases in pulse-rates and reductions in pulse pressures observed in the United Kingdom when the subjects changed posture from lying to standing, were magnified by the effect of environmental heat in Bahrein, and on the basis of previous experience (Bean and Eichna 1943, Taylor et al. 1943, Leithead 1958) it was expected that in the course of the ten-day period of acclimatisation there would be a return towards the degree of circulatory stability recorded in this country. This effect of acclimatisation did not occur and we thought it possible that dehydration, which is a potent cause of circulatory instability, was to blame. The results of the acclimatisation studies were therefore analysed to determine the relation between day-to-day fluctuations in body-weight on the one hand, and twenty-four-hour output of urine and circulatory responses to postural change, on the other. At the same time, the opportunity was taken similarly to relate daily changes in body-weight with associated sweat-rates.

As described above, on each successive day for ten days, the subjects were first weighed at least an hour and a half after starting work. The average of these daily initial weights was calculated for each subject. Twenty-four-hour samples of urine which corresponded with days when initial weights were above average were compared with those collected on days when initial weights were below average, and the same technique was applied to the weights and urines of all the subjects. Pulse increments on postural change from lying to standing, erect pulse-pressures, and sweat-rates were all grouped and compared in the same manner. The results are shown in the table. So that the subjects may be regarded as having been of a standard size, twenty-four-hour samples of urine have been expressed as ml. per 24 hours per kg. of initial body-weight, and sweat-rates have been expressed as g. per hour per kg. of initial body-weight.

It was found that on days when their weights were below average, the subjects passed less urine, and that, when they changed posture from lying to standing, they had faster pulse-rates and smaller pulse pressures than on days when their weights were above average. We have assumed therefore that their variations in weight represented fluctuations in body-water, and that at least on days when their weights were below average, the subjects were dehydrated. On these days, their sweat-rates were reduced.

Statistical analysis shows (see table) that the relations demonstrated between body-weight and urine output, circulatory stability, and rate of sweating are unlikely to have arisen by chance. The influence of water debt on sweating may have been even more significant than is suggested by the results, for other factors were acting on sweat-rates; in the absence of artificial standardisation of the activities and environments of the subjects, the nature and tempo of their duties sometimes varied con-

RELATION OF URINE OUTPUT, CIRCULATORY STABILITY, AND SWEAT-RATE TO VARIATIONS IN INITIAL BODY-WEIGHT

—	Body-weights above their individual means		Body-weights below their individual means		Difference	Standard error
	No.	Mean	No.	Mean		
24-hour urines (ml. per 24 hours per kg.)	69	9·6	68	7·5	2·1	0·6
Pulse increments on standing (beats per min.) ..	47	25·0	51	29·0	4·0	1·8
Pulse-pressures erect (mm. Hg)	49	30·0	56	25·5	4·5	1·3
Sweat-rates (g. per hour per kg.)	74	3·9	75	3·4	0·5	0·25

siderably from day to day, and so therefore did their sweat-rates. On the whole, their sweat-rates were low (daily averages were between 200–250 g. per hour) and the response of such low rates of sweating to water debt may be a further indication of the sensitivity of the relationship.

It was obviously of importance to determine whether or not urine output and rate of sweating varied in a progressive or proportional way with changes in body-weight. The daily variations in initial weight on each subject were calculated as percentage deviations from their respective averages and were then grouped into four categories—more than 0·5% above average, up to and including 0·5% above average, up to and including 0·5% below average, and more than 0·5% below. Corresponding urine volumes and sweat-rates were grouped accordingly and the same method was applied to the weights, urine outputs, and sweat-rates of all the subjects. The means for the four categories of urine output were respectively 10·1, 9·2, 7·8, and 7·1 ml. per 24 hours per kg., and the means for the four categories of sweat-rate were 3·93, 3·88, 3·56, and 3·09 g. per hour per kg. These results are shown in histogram form in figs. 1 and 2.

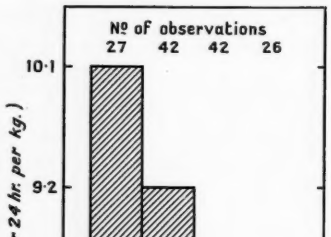

Fig. 1—Relation of urine output to variations in initial body-weights. The 18 subjects were weighed at the start of each of 7–10 successive twenty-four-hour periods.

There was a remarkable correlation between initial weights and associated twenty-four-hour outputs of urine, and the conclusion was inescapable that the subjects' weight reductions represented degrees of dehydration. There was some indication (fig. 2) that sweat-rates were reduced progressively with increasing water debt.

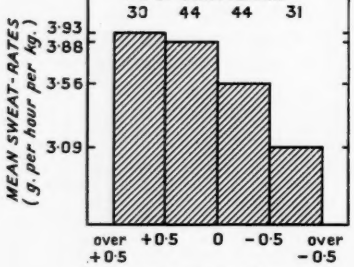

Fig. 2—Relation of sweat-rate to variations in initial body-weight. The 18 subjects were weighed at the start of a measured period on each of 8–10 successive days.

The average initial body-weight of each subject was derived from his starting weights on each of the ten days succeeding his arrival in Bahrein. There is no evidence to suggest that it was his normal or fully hydrated weight. The weights recorded before the subjects left the United Kingdom were to have supplied this information but cannot be compared absolutely with the Bahrein figures, as they were measured on balances which differed from, and were less accurate than, the one in Bahrein. It may be significant that all the subjects weighed less in Bahrein than in this country, and that according to the figures obtained, the average loss was quite considerable—2·4% of the mean United Kingdom weight. The average initial body-weights used in the construction of the table and figs. 1 and 2 may therefore represent a water debt of about 2%.

Discussion

The subjects' daily intake of all fluids averaged 6–7 pints per man, and, although they were well and obviously felt no great need of any more, this amount was not enough to maintain circulatory stability and what is usually considered to be a satisfactory output of urine. This phenomenon of voluntary dehydration, arising during work in a hot environment because the sensations of thirst are not strong enough to demand full replacement of water losses, was discussed by Adolph and Rahn (1947) who observed that the dehydration was usually corrected at mealtimes and in rest periods. Our subjects rested during the afternoon heat, but to obtain a drink of water they had to leave their billets and walk across the compound to their mess; and in the circumstances most of them preferred to stay put. It seems that, even in leisure hours, losses are not fully replaced unless palatably cool drinking-water is within easy reach.

Voluntary dehydration does not appear to be beneficial; for, as it develops, rectal temperatures and heart-rates increase; and, as our results have also shown, circulatory stability is adversely affected (Bean and Eichna 1943, Gerking and Robinson 1946, Rothstein and Towbin 1947, Ladell 1955). The effect of dehydration on sweat-rates has been much less readily demonstrated.

Lee et al. (1941) reported that the sweat-rates of hot-room subjects increased with their rate of water intake but did not imply that the increases were due to correction of dehydration. Bean and Eichna (1943) and Eichna et al. (1945) concluded from hot-room investigations that sweating was not affected by dehydration, whereas Pitts et al. (1944) found that dehydration reduced sweating. Ellis et al. (1954) observed subjects in a hot-room in Singapore and found the dehydration reduced sweating and progressively so. Robinson et al. (1956) and Pearcy et al. (1956) reported reductions of 15–20% in sweating with water debts of up to 3·4% of the body-weights of their subjects. The subjects of Buskirk et al. (1958) exercised in moderate heat in the laboratory and lost weight at 350 g. per hour when hydrated and at only 250 g. per hour when dehydrated by 5·5% of their initial body-weights. Grande et al. (1958) restricted both the fluid and the food intake of men living and working in moderate heat in the laboratory and found up to 50% reductions in sweat-rates during work, and reductions also in insensible losses during sleep, and that the rate of weight loss during work was related to the degree of dehydration. Meanwhile Gosselin (1947a and b) had found that sweat-rates were reduced by dehydration in the field (in the Californian desert) but not in the laboratory, and Ladell (1951) had remarked no significant variation in the sweat output of fully acclimatised subjects with changes in water intake, whereas later he found (Ladell 1955) reduced sweat-rates in subjects in whom the water debt exceeded 2·5 litres.

Pearcy et al. (1956) took the view that in most of the above studies, differences in experimental conditions accounted for differences in results. If so, it is hard to recognise the factors which varied significantly.

Ladell (1955) thought that failure to demonstrate a deterioration in sweat-rate with dehydration was due probably to failure to contract in the subjects a sufficiently large water debt,

but his belief is not supported by the findings either of Ellis et al. (1954) who observed the effect at water debts not greater than 1358 g., or of Gosselin (1947a) who failed to demonstrate the effect at water debts up to 9–11% of initial body-weight. Reduction of sweat-rates in dehydration has been demonstrated at high environmental temperatures with high rates of sweating by Pitts et al. (1944), but not by Bean and Eichna (1943); it has been demonstrated at a moderate environmental temperature (78°F) with both low and fairly high sweat rates (e.g., by Buskirk et al. 1958 and Grande et al. 1958, respectively).

Finally, reduction of sweat-rates with dehydration has been demonstrated sometimes but not always by brief spells of two to four hours exposure to dehydration in hot-rooms. It has not been demonstrated in hot-rooms by water deprivation lasting one to three days (Bean and Eichna 1943, Gosselin 1947a); but, despite this, chronic water debt may be a significant factor, for sweat-rates were reduced by dehydration in the subjects Gosselin (1947b) observed in the Californian desert, in our subjects in Bahrein, and in the hot-room subjects of Ellis et al. (1954) who were resident in Singapore where the outdoor climate at that time was dry-bulb 85°F and wet-bulb 79°F. We cannot find in the literature any account of failure to demonstrate the effect in tropical residents.

It is possible, however, that the differences in the results of the various studies have been due not so much to variations of experimental conditions and methods, as to the influence of physiological mechanisms not yet fully understood. Many workers have shown adaptive salt retention by sweat-glands in response to salt depletion (Dill et al. 1938, McCance 1938, Conn 1949, Robinson et al. 1950, Weiner and van Heyningen 1952). Salt retention by sweat-glands results also from administration both of deoxycortone (desoxycorticosterone) acetate and of corticotrophin (Conn 1949), and therefore sweat-glands simulate the kidneys in conservation of salt. They do not quite simulate the kidneys in conservation of water, for Robinson and his colleagues (Robinson et al., 1956, Pearcy et al. 1956) have shown that sweat-glands do not conserve water in response to the administration of vasopressin. These workers have also shown (Pearcy et al. 1956) no reduction of sweat-rate in dehydration secondary to salt depletion, and that, although salt depletion did not significantly alter the reduction of sweating in deliberate water deprivation, in some of their water-deprivation experiments slightly higher sweat-rates were observed when salt was depleted than when it was replaced. These important observations suggest that sweat-glands, while primarily concerned with heat dissipation, are sensitive also to the regulation of salt concentration in the body, and, perhaps by the mediation of aldosterone or other adrenocortical hormones, may alter accordingly their rate of water removal.

Meanwhile we may conclude that, in the absence of salt depletion, dehydration causes progressive reduction in thermal sweating. Residents in the humid tropics, who have good cause for holding forth on these matters, have long believed that their sweating is influenced directly by the amount of fluid they drink. Their belief may be based partly on fallacy, for they have observed an outburst of sweating after a long drink, and in fact this effect is transient and probably reflex in nature and is another matter altogether (Lee and Mulder 1935, Bazett 1949). There are some, however, who claim that sweat drips less profusely from their faces and into their eyes when they have deliberately restricted their fluid intake. These people should no longer be disbelieved; they can be told instead that they are trading safety for comfort and that the effects of voluntary dehydration—increased temperatures and heart-rates and reduced sweating—all predispose in the right circumstances to heatstroke.

Summary

During acclimatisation studies in 1959 on 18 young British Servicemen newly arrived in the summer heat of Bahrein, it was observed that they became moderately dehydrated. Their average daily intake of all fluids was 6–7 pints and their average twenty-four-hour output of urine during their first ten days in Bahrein was 567 ml. 48% of the twenty-four-hour urines collected were below 500 ml. and 10% were 300 ml. or less, and the specific gravities of these samples were correspondingly high. The subjects felt well and were able to carry out their routine duties, which consisted mainly of skilled and manipulative work in environmental temperatures of, approximately, dry-bulb 94°F, and wet-bulb 80°F. It was found, however, that on days when their body-weights were below average—which were assumed to be days when they were more than usually short of water—the responses of their pulse-rates and blood-pressures to postural change from lying to standing were adversely affected; on these days also, rates of secretion of both urine and sweat were significantly reduced. Further analysis of the results showed that secretion of both urine and sweat fell progressively with body-weights.

Previous reports on the effect of dehydration on sweating have often been contradictory, but the above observations support an increasing amount of evidence that thermal sweating is progressively reduced by dehydration. The phenomenon, when considered with the responses of sweat-glands to changes in body salt content, leads to the suggestion that, although sweat-glands are concerned primarily with the dissipation of heat, they simulate the kidneys in regulating salt concentration in the body by altering their rate of water removal.

We are grateful to the Director General of Medical Services of the Royal Air Force for permission to publish our findings. We wish also to express gratitude to the subjects of these investigations, to colleagues in the Royal Air Force and the Liverpool School of Tropical Medicine for administrative and professional assistance, and to Prof. Brian Maegraith and Air Commodore W. P. Stamm for their guidance and advice.

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ANHIDROSIS FOLLOWING INTRAVENOUS BACTERIAL PYROGEN

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SUDDEN cessation of sweating may precede a mild form of heat illness (Bannister 1959, Sargent and Johnson 1960). The original cases occurred among partially acclimatised soldiers, most of whom lived in a transit camp where the water-supplies were contaminated and required chlorination. Though acute gastroenteritis and other infections were common, there was no evidence that these patients were suffering from an infection. In particular the cessation of sweating was not associated with shivering and only in one case was there an accompanying sensation of chill. However, the possibility remained that an occult infection might have prevented sweating, for Park and Palmes (1948) showed that, in subjects exposed to an artificial hot dry environment, evaporative heat loss was markedly reduced during fevers caused by injections of typhoid vaccine.

The experiments described in this paper were devised to study quantitatively the effect of injections of a purified bacterial polysaccharide on the sweat-rate of healthy subjects exposed to an artificial hot humid climate, such as existed in Aden. An attempt was made to imitate the syndrome of acute anhidrotic heat-exhaustion by giving a dose of pyrogen which reduced sweating without causing a rigor. Observations were also made on the effect of a change of environmental temperature on the response to a standard dose of pyrogen. Park and Palmes (1948) found that the variation of the febrile response after injections of typhoid vaccine in different subjects at several environmental temperatures was so great that they were only able to conclude that " no tendency was noted for fevers to be more severe in hot surroundings ". If in fact a greater febrile response occurred at a higher environmental temperature, this might provide one possible explanation of the heatstroke syndrome.

Method

The four subjects were healthy male volunteers, aged 27–36. One (R. B.) had returned from Aden 9 months previously.

Two subjects took part in each of eleven experiments; on each occasion one subject was given pyrogen by intravenous injection while the second acted as a control. The pyrogen used was a purified lipopolysaccharide obtained from *Salmonella abortus equi* (' Pyrexal ', Wander) in doses of 0·1 to 0·45 μg. For periods of 3–6 hours both subjects sat nude in a hot chamber which was maintained at a basic effective temperature (see Bedford 1946) of 92–95°F in ten experiments and at 73°F in one. In each experiment the subjects were weighed in the hot chamber at intervals of 15 minutes, on a balance sensitive to 5 grammes. The subject mopped his body surface gently with a towel for a minute before each weighing.

Oral and rectal temperatures were recorded by mercury in glass thermometers whose readings did not differ by more than ±0·1°F from the readings of a standard thermometer when heated together in a water-bath from 98° to 105°F. The same thermometers were used by the same subjects throughout each experiment. Temperature recordings were made immediately after each weighing and in some experiments more frequently between weighings.

During each experiment estimates of sweat-gland activity were made by the plastic impression method (Sutarman and Thomson 1952). When sweating stopped, the effect of an intracutaneous injection of 0·01% methacholine chloride (' Amechol ') on sweat-gland activity was studied.

Fluid losses were estimated from weight losses during the experiments and were replaced half-hourly by drinking measured volumes of tap-water at the hot-chamber temperature. Two 0·5 g. salt tablets were given with each 500 ml. of water.

Results

In all four subjects a complete cessation of sweating lasting from 7 to 60 minutes occurred between 55 and 105 minutes after the intravenous injection of pyrogen (see table). On all occasions on which the cessation lasted sufficiently long for the injection to be given and sweat impressions taken, the sweat-glands were stimulated to activity by an intracutaneous injection of methacholine chloride after the cessation (fig. 2).

EFFECT OF INTRAVENOUS BACTERIAL PYROGEN ON BODY TEMPERATURE AND SWEATING

Experiment number	Days after first experiment	Subject	Control	Dose of pyrogen (μg.)	Change of body temperature 2 hours after pyrogen (°F)*	Latency of initial change of oral temperature (minutes)	Decline of sweating †	Complete cessation of sweating	Latency of cessation (minutes)	Activation by intracutaneous methacholine chloride (where given)	Duration of cessation of sweating (minutes)
1	0	R. B.	J. M.	i 0·1 ii 0·2	0·2 2·9	95 60	+ +	0 +	.. 60	.. +	.. 50
2	10	R. B.	J. M.	0·25	0·4	80	+	+	80	..	10
3	89	R. B.	W. L.	0·30	1·2	80	+	0	..	..	..
4	92	R. B.	G. N.	i 0·15 ii 0·25	0 3·4	80 55	0 +	0 +	.. 55	.. +	.. 60
5‡	112	R. B.	J. M.	i 0·15 ii 0·25	0·2 4·0	105 60	.. ..	.. ..	.. ..	.. ..	.. ..
6	124	R. B.	G. N.	0·45	1·0	90	+	+	90	+	60
7	18	J. M.	R. B.	0·2	0·1	90	+	+	90	..	7
8	40	J. M.	R. B.	0·3	0·1	95	+	+	90	..	15
9	47	W. L.	R. B.	0·2	0·5	100	..	..	..	..	..
10	43	W. L.	R. B.	i 0·1 ii 0·2	0·7 2·1	85 85	+ +	0 +	.. 85	.. +	.. 45
11	130	I. McC.	R. B.	0·15	0	105	+	+	105	+	18

* Difference between body-temperature change in test subject and control, measured by subtraction of the difference between the mean temperature $\frac{(\text{oral}+\text{rectal})}{2}$ of subject and control at the time of the pyrogen injection from the difference two hours after the injection.

† Decline defined as a sweat loss (recorded as weight loss) two hours after the pyrogen injection less than 60% of the peak sweat loss.
‡ Mean effective environmental temperature 73°F.

Initial and Single Injections of Pyrogen under Uncomfortably Hot Conditions

In subject R. B. initial doses of 0·1 μg. of pyrogen (experiment 1) and 0·15 μg. (experiment 4) failed to cause either a febrile response or a cessation of sweating within 2 hours. However, 0·25 μg. (experiment 2) caused a small febrile response and a cessation of sweating lasting 10 minutes, both responses occurring after a latent period of 80 minutes (fig. 1c). In an experiment 11 weeks later (experiment 3) 0·30 μg. of pyrogen caused only a mild febrile response and a reduction of sweating without complete cessation. In a further experiment 4 weeks later (experiment 6) 0·45 μg. caused a febrile response and a gradual reduction leading finally to a cessation of sweating (fig. 1d).

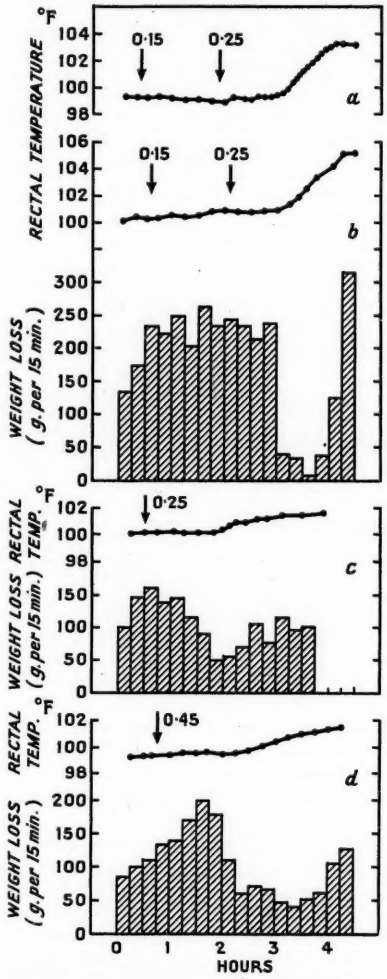


Fig. 1—The effect of bacterial pyrogens on body temperature and weight loss, under comfortably warm conditions (experiment 5) and under excessively hot conditions (experiments 4, 2, and 6).

From above downwards:

a. Experiment 5. Rectal temperature after two doses of pyrogen (0·15 μg. and 0·25 μg.), mean effective temperature 73°F.

b. Experiment 4. Rectal temperature and weight loss after two doses of pyrogen (0·15 μg. and 0·25 μg.), mean effective temperature 94°F.

c. Experiment 2. Rectal temperature and weight loss after 0·25 μg. pyrogen, mean effective temperature 93°F.

d. Experiment 6. Rectal temperature and weight loss after 0·45 μg. pyrogen, mean effective temperature 93°F.

Subject: R. B.
Abscissa: Time (hours).
Ordinate: Sweat loss reckoned as weight loss (g. per 15 min.). Rectal temperature (°F).

In the second subject (J. M.) sweating ceased completely for a short time, after a single injection of pyrogen, on two separate occasions (0·2 μg. and 0·3 μg., experiments 7 and 8).

In the third subject (W. L.) a single injection of 0·2 μg. of pyrogen produced a mild fever without a significant change in the sweat-rate (experiment 9).

In the fourth subject (I. McC.) a single injection of 0·15 μg. of pyrogen caused a mild fever and a total cessation of sweating lasting 18 minutes. The latency of both responses was 105 minutes (experiment 11).

Thus cessation of sweating occurred on five occasions after a single injection of pyrogen. The mean body temperature at the moment of total cessation of sweating was 99·9°F (range 99·4–101·0°F). Symptoms at this time were in all experiments a mild headache and fatigue, and on three occasions nausea, with vomiting on two of these occasions.

In these experiments small doses of pyrogen caused a cessation of sweating at the onset of a mild rise in body temperature (less than 1·2°F on all occasions). Sweating ceased over the range of body temperature which normally causes profuse sweating. Its cessation was the effect of the pyrogen and not secondary to the rise of body temperature, because sweating returned while the body temperature remained raised.

Double Injection of Pyrogen under Uncomfortably Hot Conditions

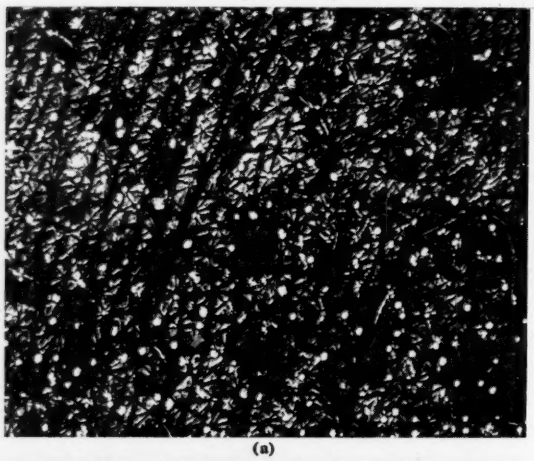
In three experiments two injections of small doses of pyrogen were given at an interval of 90 minutes. Neither dose would by itself have been expected to have more than a trivial effect on body temperature, but on each occasion the double injection produced exaggerated febrile and anhidrotic responses.

In experiment 1 (subject R. B.), 0·1 μg. of pyrogen was followed by 0·2 μg., given 90 minutes later. 60 minutes after the second injection, the oral and rectal temperatures rose by more than 3°F and sweating stopped for 50 minutes. The rate, magnitude, and latency of the response to similar injections were unchanged three months later (experiment 4, R. B., see fig. 1b). On this occasion when the rectal temperature reached 105·0°F, profuse sweating suddenly occurred and the temperature fell. In experiment 10 (subject W. L.) exaggerated febrile and anhidrotic responses followed injections of 0·1 and 0·2 μg. of pyrogen given at an interval of 90 minutes. The effect was comparable to the exaggerated response to a double injection produced in the first subject on two occasions.

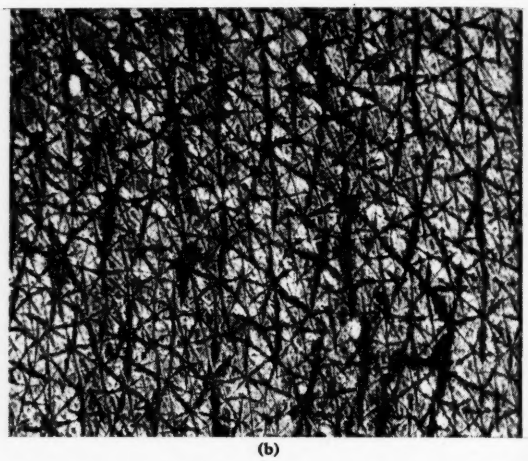
Though in the double-injection experiments a mild headache was the only symptom, apart from fatigue, at the moment of cessation of sweating, subsequently other symptoms were noted. Nausea was marked and in experiment 10 the subject's skin grew pale, with a "gooseflesh" appearance, and he complained of a sensation of chill. His blood-pressure fell to 90/75 after sweating stopped and there was a transient fall in oral temperature. He did not faint, and these changes in skin appearance and blood-pressure persisted for 15 minutes only, though sweating did not return for 45 minutes.

Double Injection of Pyrogen under Comfortably Warm Conditions

In experiment 5 (subject R. B.) the double-injection procedure of experiment 4 was repeated under comfortably warm conditions at an effective temperature maintained at 73°F (see fig. 1a). There was a rise in body temperature comparable in rate, magnitude, and latency, though body sweating was not observed at any time during the $4^1/_2$ hours' exposure. At the onset of the fever violent shivering occurred and persisted for 65 minutes. The final temperature reached under uncomfortably hot conditions was higher than under comfortably warm conditions, probably because the rectal temperature was already higher at the onset of the febrile response. Further observations on the effect of changes of environmental temperature on the responses of the other subjects were not made, because the discomfort caused was too great.



(a)



(b)

(c)

Fig. 2—Specimens of plastic skin impressions on subject R. B. during exposure to a mean effective temperature of 93°F. (×10.)

a. Control plastic impression (weight loss 180 g. per 15 min.).

b. Plastic impression after cessation of sweating caused by double dose of pyrogen (weight loss 20 g. per 15 min.).

c. Plastic impression 10 minutes later than B, after intracutaneous injection of methacholine chloride (site of injection corresponds to upper half of photograph).

Discussion

Ætiology of Acute Anhidrotic Heat-exhaustion

The results of these experiments make it likely that in hot humid climates the first and sometimes the chief symptom of an infection is sudden cessation of sweating under conditions in which sweating is normally profuse. This is in contrast to the chill, the rigor, and the fever itself, which are the more obvious general symptoms of an infection in a temperate climate. For this reason it is possible that in some of the subjects in Aden in 1958 acute anhidrotic heat-exhaustion was caused by infection which resulted in the liberation of a pyrogen. The duration of the anhidrosis and the extent of the rise of body temperature resulting from an occult infection might be expected to depend on the rate of liberation and the potency of the pyrogen and the tolerance of the subject. Since, in the present experiments, intracutaneous injections of methacholine chloride apparently reactivated the sweat-glands after the cessation of sweating, it is probable that the pyrogen in some way caused a failure of stimulation of the sweat-glands by a "central" nervous mechanism (see Wilson 1934) as opposed to sweat-gland "fatigue" (Thaysen and Schwartz 1955).

Since the description of twelve cases of acute anhidrotic heat-exhaustion (Bannister 1959), Sargent and Johnson (1960) have described four further cases. They differ only in emphasising the return of sweating after drinking, though in four out of six of the original patients facial sweating was noted on clinical examination within 5 minutes of drinking a pint of fluid. Of Sargent and Johnson's four cases one had pharyngitis and cervical and axillary lymphadenitis and a second "a slightly injected left ear drum". Thus the possibility that a mild infection may have contributed to the anhidrosis in two of their cases cannot be excluded.

Ætiology of Heat Hyperpyrexia and Heatstroke

In the present experiments rectal temperatures both before and after the febrile response to the same dose of pyrogen were nearly 2°F higher at the high environmental temperature than at the lower environmental temperature. Hence a subject given a dose of pyrogen in a hot environment may be more likely to become "hyperpyrexial" than a subject given the same dose in a cool environment, although the actual rise of body temperature may be similar in the two environments.

In the present experiments the dry-bulb temperature (mean 100·5°F) was similar to the body temperature; and so, after the cessation of sweating, there was no rapid heat gain from the environment. However, dry-bulb and globe temperatures in the sun may reach and exceed 120°F in the desert and may be tolerated without harm provided heat loss through sweating occurs. Robinson (see Newburgh 1949) has shown that at a dry-bulb temperature of 120°F a man at rest must lose about 225 calories per sq. metre per hour, by sweating to remain in thermal equilibrium. Under these circumstances, if sweating ceased, heat would be gained rapidly from the surroundings, causing the body temperature to rise at a rate of about 9°F per hour, and to this must be added the rise due to increasing endogenous heat production of the body. In one of the present experiments, with only slight heat gain from the surroundings, the rectal temperature rose to 105°F in 60 minutes after a double pyrogen injection, before sweating suddenly returned. At a dry-bulb temperature of 120°F the same temperature rise would occur almost

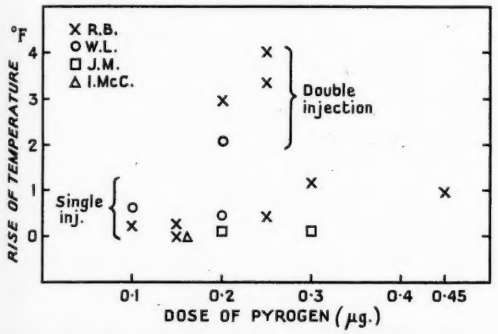


Fig. 3—The febrile response to single and double doses of pyrogen. (The difference between the body temperature change in test subject and control, measured as recorded in footnote to the table.)

three times as fast, and it seems possible that after the appropriate temperature rise caused by a pyrogen, sweating might not return sufficiently rapidly in all subjects to prevent the body temperature reaching the hyperpyrexic range and heatstroke might supervene. However, in the anhidrosis of heatstroke subcutaneous injection of pilocarpine failed to cause sweating (Hearne 1919) whereas in pyrogen-induced anhidrosis intracutaneous injections of methacholine chloride always provoked a local response.

These experiments suggest one common cause of anhidrosis in hot climates, though others may well exist. The results provide an alternative to Ladell's hypothesis (1957) that " hyperpyrexia is fundamentally a physiological phenomenon; when the temperature rises, sweating stops and cooling ceases ". In these experiments profuse sweating occurred at 105°F at the time when the effect of the pyrogen was subsiding but before body temperature had fallen to normal. It seems likely that in some cases of hyperpyrexia and heatstroke, as in acute anhidrotic heat-exhaustion, anhidrosis is the primary event.

The Action of Pyrogens

Though the action of pyrogens in man and animals has been extensively studied (Bennett and Beeson 1950, Cranston et al. 1956, Eichenberger et al. 1955, Snell et al. 1957, Petersdorf and Bennett 1959), there is no record of the effect of repeating within 2 hours a small dose of pyrogen which is itself almost without effect in causing fever. In the present experiments this produced an exaggerated febrile response. By comparison with the fever caused by a single injection of a larger dose, two injections caused a higher fever (fig. 3). Thus the first dose in some way increased the response to the second dose, and this mechanism is likely to occur in natural fever with continuous or intermittent production of pyrogen.

Grant and Whalen (1953) obtained evidence that the fever-producing effect of a pyrogen in animals might be due to the release of an intermediate substance (" endogenous pyrogen "). Gerbrandy et al. (1954) showed that in man incubation of the pyrogen with the patients' own blood in vitro reduced the latency for the rise of oral temperature from 71 minutes to 19 minutes, which suggested that endogenous pyrogen was produced in vivo after about 50 minutes. The cause of the delay in action of endogenous pyrogens is unknown, but it may be due to the formation of a further intermediate substance or may represent the time taken for the endogenous pyrogens to diffuse to the site of action in the cell (Pickering 1958).

The response to the second injection of pyrogen in the present experiments had a latency of 55–60 minutes in three experiments on one subject and 85 minutes in a second subject. Hence it is possible that the intermediate reaction resulting in the formation of endogenous pyrogen still took place at the normal rate. In view of the present ignorance about the action of endogenous pyrogen, it is perhaps unwise to speculate on possible explanations of the increased febrile response to the second injection. However, the endogenous pyrogen produced by the first injection may (1) neutralise some substance in serum which inactivates endogenous pyrogen (possibly similar to that described by Rowley et al. in 1956, which splits bacterial polysaccharide); or (2) accelerate an intermediate reaction of endogenous pyrogen; or (3) increase the rate of diffusion of endogenous pyrogen into the cell.

Temperature Regulation During Artificial Fever

Park and Palmes (1948), extending the work of Barr et al. (1922), studied temperature regulation in man at different ambient temperatures during fever caused by typhoid-vaccine injections. They drew the general conclusion, which is confirmed by the results of the present experiments, that the pattern of temperature regulation during fever is governed by the thermal nature of the environment and the strength of the pyrogenic stimulus.

In the present experiments the same doses of pyrogen, given to one subject at high and low environmental temperatures, produced rises in body temperature comparable in latency, rate, and magnitude, though both the initial and final rectal temperatures and the effector mechanisms by which the rises were produced were different. At the high temperature the rise was likely to have been caused principally by a reduction of heat-loss resulting from cessation of sweating. At the low temperature it was caused mainly by an increase in heat-production caused by violent shivering.

A pyrogen injection produces changes which are similar to those caused by exposing a healthy person to cold, and it is likely that, as in " natural " fever, the level of setting of the thermotaxic mechanism is raised. The extent to which the setting of the thermotaxic mechanism was altered in these experiments seemed to be unaffected by a large change in environmental temperature, though the initial rectal temperature was higher in the hotter environment. At the low environmental temperature prompt shivering occurred, which was absent after the same change in the setting of the thermotaxic mechanism at the high temperature. Thus the difference between the body temperature and the new level of the setting of the thermotaxic mechanism is abolished at a similar rate, independently of environmental temperature within a certain range. This implies the presence of some kind of thermoreceptor cells relaying information about either the environmental temperature or the rate of rise of body temperature, or both, and resulting in a modification of the temperature-regulating mechanisms appropriate to the particular environment.

Since in our experiments sweating was studied while the body temperature rose as a result of pyrogen injections, the results cannot be compared with those of Macpherson (1959), who reported that the sweat-loss of a single subject in a hot chamber was unaffected during a long-continued fever due to a respiratory infection.

Summary

1. In four subjects exposed to an artificial hot environment, intravenous injections of bacterial pyrogen caused sudden cessation of sweating lasting from 7 to 60 minutes. During the anhidrosis, sweat-glands were apparently activated by an intracutaneous injection of methacholine chloride.

2. The rise of body temperature after a pyrogen injection occurred with the same latency as the cessation of sweating, and on seven out of eight occasions when the response was evoked it was not associated with a chill or rigor.

3. These observations suggest a possible cause of acute anhidrotic heat-exhaustion and of hyperpyrexia and heat-stroke under critically hot environmental conditions.

4. A marked febrile response and prolonged cessation of sweating were caused by two injections, at an interval of $1^1/_2$ hours, of doses of pyrogen which singly evoked only a trivial response. Possible reasons for this are discussed in the light of what is known of the action of pyrogens.

5. The rise of body temperature caused by the same doses of pyrogen in one subject was similar at two environmental temperatures differing by 20°F, though an additional effector mechanism (shivering) was invoked at the lower temperature. The possible theoretical significance of this observation is discussed.

This work was undertaken during tenure of an academic registrarship, while attached to the Academic Unit, the National Hospital, Queen Square.

I am grateful to Prof. G. P. Crowden for permission to use the hot chamber at the London School of Hygiene and Tropical Medicine. My thanks are due to the subjects for their cooperation in these experiments, to Mr. James MacNaughton for his technical assistance, and to Dr. K. E. Cooper who provided 'Pyrexal' from supplies given to him by A. Wander Ltd. I should also like to thank Sir George Pickering for his encouragement and Dr. W. S. Ladell for helpful criticism of the manuscript.

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"Moral conduct is involved only when a genuine choice between actions is possible. We hold that man has free-will, through introspection and through what others tell us, while on the legal plane we accept as valid the distinction between a person being responsible or irresponsible for his actions, even though it may be hard to decide in certain cases. But no test or experiment can be devised to determine whether another animal has free-will. Sometimes we may see it delay before acting, but then the biologist may say that it was subject to conflicting drives, one of which proved strongest."
—DAVID LACK, F.R.S., *Nature, Lond.* July 9, 1906, p. 98.

ELASTIC-STOCKING COMPRESSION AND VENOUS BLOOD-FLOW

EFFECT IN THE LOWER LIMB

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PULMONARY embolus is still a great potential killer in clinical practice, and the embolus most often arises from thrombosis in the veins of the legs or pelvis. Thrombosis has been attributed to venous stagnation, to damage to the endothelial lining, and, in surgical patients, to a natural increase in blood coagulability after operation. The last two factors can be benefited by care of the legs whilst the patient is on the operating-table, and by prudent use of anticoagulants prophylactically in patients who are prone to pulmonary embolus.

In an attempt to increase the rate of flow in the veins Wilkins et al. (1952, 1953) suggested using elastic stockings. A protracted clinical trial of elastic stockings and stockinet in alternate patients showed a definite decrease both in the morbidity-rate from venous thrombosis and in the fatality-rate from pulmonary embolus in those patients protected by compression of the legs. But these workers used elastic stockings empirically. We therefore decided to measure whether such compression did in fact increase the rate of blood-flow in the leg veins.

The rate of flow can be measured in several ways. Stanton et al. (1949) measured venous flow using Evans-blue, but this technique proved clumsy, and was soon replaced by radioactive isotopes (Osborn and Wright 1949). We modified Osborn and Wright's method by using human albumin labelled with ^{132}I instead of ^{24}Na. Albumin labelled with ^{132}I was chosen because: (1) the possibility of diffusion from the vein during the short period of the test is much less than with simpler substances which are known to diffuse, and therefore it gives a more accurate measure of blood-flow; and (2) half-life of ^{132}I (2·4 hours) reduces the radiation dose delivered to the patient. The albumin was labelled with ^{132}I by the method of Veall et al. (1955).

The Investigation

The Patients

Eighteen men and thirteen women were randomly selected mainly from those awaiting operation, but a few who were recovering from minor operations—such as excision of the upper half of the pinna, or breast biopsy—were included. Several outpatients also agreed to the test. The patients were aged 32–72, with an average of 48 years. The ages of nineteen patients were between 40 and 59. None of them had varicose veins.

Method

The maximum calf measurement was taken with the patients sitting on the end of a table, and their feet resting on a stool. 'Eesiness' full-length seamless one-way-stretch elastic stockings, which exert concentric pressure of 10 mm. Hg, were used. (The small size for calves with a circumference of 11–$12^1/_2$ in., the medium size for calves of $12^1/_2$–15 in., and the large size for calves measuring more than 15 in.)

The pressure of the stockings was measured by the following technique. Two finger-stalls, without their rims, were connected to size-1 polyethylene tubes by tying their bases over the tubes with

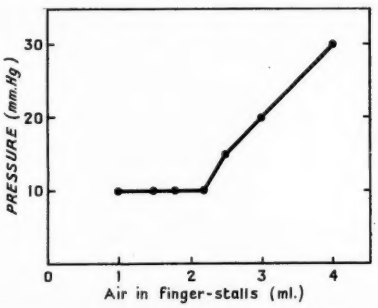

Fig. 1—Measurement of pressure exerted by elastic stockings, using finger-stalls.

fine wire, so as to produce an airtight fit. The polyethylene tubes were connected to a mercury manometer via a Y-connection. A 20-gauge needle on a 5-ml. syringe, with a two-way tap, was introduced into the rubber tubing between the Y-connection and the manometer. After filling the dead-space, gradually increasing amounts of air were injected into the finger-stalls, which were placed between the medial and lateral aspects of the calf and the elastic stocking, and pressure readings were taken. By plotting pressure against volume of air injected into the finger-stalls, fig. 1 was obtained. There was no distortion of limb contour until 2·5 ml. or more of air had been injected. It can be seen, therefore, that the stocking exerted a pressure of 10 mm. Hg on the calf, and that pressures above this level were due to excess air producing abnormal stretching of the elastic.

The right leg was stockinged, and the left was used as control. Payling Wright and Osborn (1952) have shown that the rate of flow is the same in both legs of any normal person. While still in the sitting position, fine 18-gauge needles were inserted into suitable veins on the dorsum of each foot, and the lumina were kept open by wire stillettes. The needles were lightly strapped to the foot, and the elastic stocking on the right leg was so arranged as to cover the needle point.

The patient was then helped into the supine position, and two Geiger-Muller counters (G.10Pb) were arranged—one over the ankle-joint, and one at right angles to the long axis of the limb, centred over the femoral artery at the level of the inguinal ligament (fig. 2). The counter over the femoral vein was shielded with 3 cm. of lead in which was cut a rectangular slit 2·5 × 11 cm. Both counters were connected through probe units to rate-meters ('Ekco' type no. 1138A). The output of the rate-meters was fed into a double channel recording milliammeter ('Evershed Vignoles' double-channel recording milliammeter), the paper being driven at the rate of 9 in. a minute. The stillette in the needle was replaced by a syringe, containing 10 μC of ^{132}I-labelled albumin in a volume of 1 ml., and the drum of the recording milliammeter was set revolving. When a steady base line of activity was established the radioactive albumin was injected as quickly as possible. Counting was continued until a significant rise was seen in the count-rate over the femoral vein. The counters were then moved to the other leg, and the experiment was repeated. There was no routine order of examination of the limbs, sometimes the right and sometimes the left being examined first. After the first recording the distance between the counters was taken with a tape-measure which ran over the adductor tubercle much as does the long saphenous vein. When the second leg was examined the counters were placed the same distance apart as before. The first injection was not given until the patient had rested supine with the calves unsupported for 15 minutes.

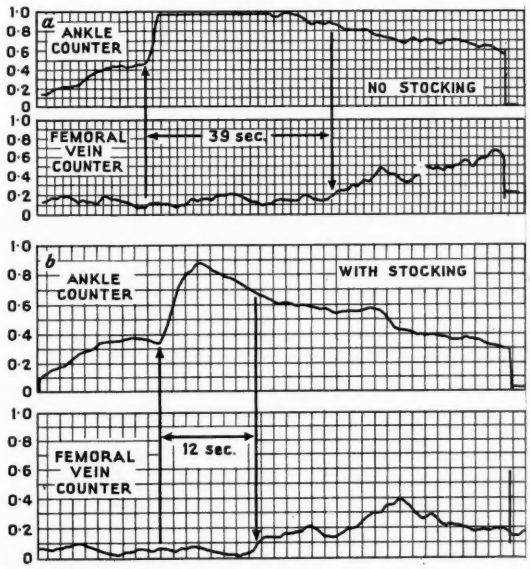

Fig. 3—(*a*) typical tracing from the left leg; and (*b*) tracing from the right leg (with stocking) of the same patient.

Fig. 2—The apparatus used, showing the collimator used to shield the counter over the femoral vein.

To determine the time taken for the albumin to pass the two counters, and hence to calculate the rate of blood-flow in the leg, the distance on the traces between the points where the count-rates started to increase in the upper and lower counters was measured and converted into seconds (see fig. 3). This method of measuring the rate of flow from the traces has also been used by Cotton et el. (1959).

Results

The table shows that the rate of blood-flow was greater in the stockinged limb in twenty-eight of the thirty-one patients studied. In twenty-two (71%) compression produced a rate of flow which was more than double that in the control limb. One patient had the same rate of flow in both limbs, and only two (6·6%) had a greater flow in the control limb.

RESULTS

Case no.	Age (yr.)	Sex	Rate of flow with stocking (cm. per sec.) (A)	Rate of flow without stocking (cm. per sec.) (B)	Ratio A/B
1	32	F	4·9	3·25	1·51
2	32	F	1·14	0·42	2·7
3	32	M	3·4	1·3	2·6
4	32	M	2·5	2·1	1·2
5	35	M	2·7	0·8	3·4
6	39	M	1·2	0·6	2·0
7	40	F	5·9	2·5	2·4
8	40	M	6·15	5·75	1·07
9	43	F	0·6	0·18	3·33
10	45	F	0·77	0·22	3·5
11	45	F	1·5	0·5	3·0
12	45	M	2·9	1·4	2·07
13	46	F	2·3	0·8	2·9
14	47	M	4·5	1·5	3·0
15	48	F	2·0	0·33	6·05
16	48	F	1·0	0·9	1·1
17	49	M	0·74	0·31	2·4
18	50	M	1·6	0·6	2·7
19	51	F	2·6	1·5	1·7
20	51	M	1·7	0·5	3·4
21	51	M	1·1	0·21	5·2
22	51	M	0·97	0·19	5·1
23	53	M	1·7	0·73	2·3
24	53	F	0·7	0·3	2·3
25	54	M	0·7	0·3	2·3
26	54	M	0·4	0·53	0·75
27	60	F	1·5	0·7	2·14
28	63	F	0·46	0·42	1·1
29	65	M	0·6	0·97	0·62
30	72	M	0·5	0·25	2·0
31	76	M	1·1	1·1	1·0

Discussion

It is currently believed that (elastic stocking) compression of the leg decreases the rate of flow in the veins. Halperin et al. (1948) showed that a pressure of 30 mm. Hg had this effect, but when milder pressure was applied the linear velocity increased because of the disproportionately greater decrease in cross-sectional area of the venous bed than in the volume of arterial blood-flow into the limb. These workers suggest that a pressure of 20 mm. Hg is optimal for the greatest effect on circulation. We found that the pressures exerted by the stockings was in the neighbourhood of 10 mm. Hg.

In one of our two patients (cases 26 and 29) in whom the rate of flow was greater in the control limb, we were doubtful whether the injection in the stockinged limb was in fact intravenous, because the counter over the ankle showed an extremely slow fall in count-rate after the injection had been given. In the other patient there was no obvious reason for the reversal of rate of flow.

In general, the rate of blood-flow was greater in younger patients.

Summary

Venous flow-rates in the leg can be measured by means of ^{132}I-albumin.

In thirty-one randomly selected patients the rate of flow was measured in both legs, one being subjected to concentric compression by a one-way-stretch elastic stocking. The stockinged leg had a more rapid flow than its fellow in all but two patients, and the rate was more than doubled in 71%.

The results show that the use of an elastic stocking increased the rate of blood-flow in the legs of most of the patients investigated. This supports the view that prophylactic use of elastic stockings, particularly in middle-aged patients who are awaiting operation, should decrease the morbidity from venous thrombosis and subsequent pulmonary embolus.

We are grateful to Prof. Ian Aird for permission to study his patients, and for helpful criticism; to Dr. Elizabeth Jones and her staff who labelled the human albumin, which was very kindly supplied by the Lister Institute; and to Dr. Leon Szur and Dr. J. R. Mallard for their helpful comments.

We are indebted to the medical illustration department of Hammersmith Hospital for the photographs and graphs. The 'Eesiness' stockings were manufactured by E. Sallis, Ltd., of Old Basford, Notts.

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NEOMYCIN-RESISTANT STAPHYLOCOCCI

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DESPITE extensive use of neomycin for preoperative bowel sterilisation, treatment of hepatic coma, and topical antimicrobial therapy, resistance of staphylococci to this antibiotic has not been a serious problem (Knight and Holzer 1954, Hein 1957, Waisbren and Stretitzer 1959, Finland et al. 1960, Petersdorf et al. 1960). Only one institution has reported resistant strains (Petersdorf et al. 1960). The occurrence and spread of neomycin-resistant staphylococci among patients at a large general city hospital is the subject of the present paper.

At the Minneapolis General Hospital since 1953, as part of a staphylococcal control programme (Hitchcock et al. 1958), antibiotic sensitivity tests have been performed on nearly all strains of coagulase-positive staphylococci isolated from patients. In February, 1959, a strain of *Staphylococcus aureus* isolated from a patient in the outpatient department was found to be resistant to neomycin (5 μg. neomycin per disc). (This was the first strain cultured at this hospital which showed this resistance.) In April, 1959, strains from 4 patients in the hospital were resistant, and in May, 1959, the number was 24. 21 of the 24 patients were on a single station (station 21, a three-ward surgical station; average admission-rate 100 patients per month). Neomycin-resistant strains of staphylococci persisted, and by Dec. 31 the number of patients infected with them had risen to 144. Of the 1248 strains of coagulase-positive staphylococci cultured and assayed for antibody sensitivity during the year 20·8% were resistant to neomycin.

Patients and Methods

In 1959 there were 10,134 admissions to the hospital, about 20% of which were to surgery or one of the surgical specialties. The buildings have been described elsewhere (Hitchcock et al. 1958).

In the main diagnostic laboratory all cultures identified as *Staph. aureus* were tested for coagulase by the slide agglutination technique. Cultures with coagulase-positive staphylococci were sent to the medical research laboratory, where since 1953 all antibiotic sensitivity tests have been performed by one of us (M. C.).

Since January, 1958, the disc method has been used for most of the antibiotic sensitivity testing. A loopful of the

TABLE I—ANTIBIOTIC RESISTANCE OF STAPHYLOCOCCI AT MINNEAPOLIS GENERAL HOSPITAL, 1958–59

Antibiotic	Antibiotic concentration in discs	Percent of cultures resistant	
		1958 (1049)*	1959 (1248)*
Tetracycline	5 μg.	59·3	56·8
Streptomycin	10 μg.	57·7	55·0
Chloromycetin	5 μg.	30·8	40·4
Penicillin	2 units	78.1	80·0
Bacitracin	2 units	2·0	12·7
Erythromycin	2 μg.	37·8	43·8
Neomycin	5 μg.	0	20·8
Novobiocin	5 μg.	18·9	31·3
Oleandomycin	5 μg.	14·6	15·9

* Number of cultures of coagulase-positive staphylococci.

colony to be tested was transferred to a tube of tryptose soy broth and the inoculum streaked on a plate containing Muller-Hinton medium. The antibiotic discs * were then applied by means of an automatic dispenser. The plates were incubated for 18–24 hours at 37°C and a clear zone around the disc of greater than 2 mm. was taken to indicate sensitivity of the organism to the concentration of antibiotic in the disc. The concentration of neomycin in each disc was 5 μg., and in this paper the strains described as neomycin-resistant are those resistant to the 5 μg. discs.

The neomycin resistance of selected strains was confirmed by tube dilution technique. Dilutions of antibiotics in physiological saline were used for testing the sensitivity of an 18–24 hour broth culture of the organism. The broth culture was diluted 1 to 100 with tryptose soy broth and 0·5 m.l of the bacterial inoculum was incubated with 0·5 ml. of the antibiotic dilution. The mixture was incubated for 18–24 hours at 37°C, and the first clear tube was read as the minimal inhibiting concentration of the antibiotic.

Results

The percentage of staphylococcal cultures resistant to the antibiotics tested in 1958 and 1959 are shown in table I. There was a significant increase in the number of cultures resistant to neomycin, bacitracin, and chloromycetin, and novobiocin, with no apparent change in therapy or routine procedures in the hospital during this time.

In February, the first strain of neomycin-resistant staphylococci was isolated from the draining axillary lymph-node of a patient treated in the outpatient department for infected lichen planus. He had been treated with 1% neomycin ointment for one month before the culture.

In April, 1959, the first strain of neomycin-resistant *Staph. aureus* was isolated from a patient in the hospital. This culture was from the draining postoperative wound of a patient on station 21 who had received neomycin orally for bowel sterilisation prior to surgery and whose infected wound was treated with neomycin packs.

During May, 1959, neomycin-resistant *Staph. aureus* were cultured from 24 patients in the hospital—21 of them from station 21. 7 of these patients had received neomycin, either for bowel sterilisation or as local antibiotic treatment, before the culturing of neomycin-resistant staphylococcus. 25 of the neomycin-resistant strains, cultured from as many patients, were checked by the tube dilution method, and all these strains were resistant to a concentration of neomycin 50 μg. per tube. Before 1958, when all the antibiotic sensitivity tests were performed by the tube dilution technique, none of the strains were found to be resistant to 50 μg. of neomycin (Spink 1956). Since last August, kanamycin ('Kantrex') has been included in the antibiotic sensitivity tests, and, as was to be expected (Kunin et al. 1958), there was complete cross-resistance.

Of the 144 patients from whom neomycin-resistant staphylococci were isolated in 1959, 58 had been, or were being, treated with neomycin. No attempt was made to ascertain the total number of patients in the hospital infected with or carrying a neomycin-resistant strain of staphylococcus; cultures were usually obtained from patients with definite signs of infection, and antibiotic sensitivity tests were done routinely on all strains of coagulase-positive staphylococci. The figure compares the number of patients with neomycin-resistant staphylococci in station 21 with the number on other wards. Though the organism was obtained from nearly all of the other stations in the hospital, no other station had more than 3 patients with this strain during one month.

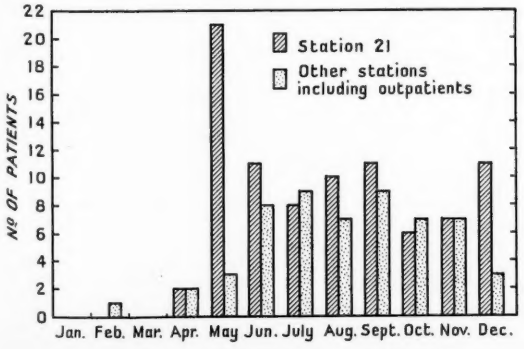
The sources of the cultures containing neomycin-resistant staphylococci are shown in table II. While most of the isolates were from "open" lesions (i.e., wounds, abscesses, or infected bedsores), many were from "internal sources" (urine, stools, and blood). Table II shows only the source of the first culture from each patient; but in 27 cases neomycin-resistant organisms were cultured from two or more parts of the body.

TABLE II—SOURCE OF NEOMYCIN-RESISTANT STAPHYLOCOCCI

Source	Number of patients
Blood	4
Surface infection	80
Sputum	28
Stool	7
Urine	15
Peritoneal cavity	4
Pleural cavity	1
Nose or throat	5

12 of the isolates were sent to the Communicable Disease Center, Chamblee, Georgia, for typing. Though there was no lysis with any of the 24 phages when used at the critical test dilution, all the organisms were lysed by phage-type 54 at a concentration 100 times higher.

* B. B. L. Sensi Discs: Purchased from the Baltimore Biological Laboratories, Baltimore, Maryland.



Patients with neomycin-resistant staphylococci, 1959.

Discussion

Shortly after the introduction of neomycin for clinical use in 1949, its toxic side-effects were recorded and its systemic administration was largely discontinued (Waisbren and Spink, 1950). Perhaps because of this restriction, it has been effective against staphylococcal infections for a longer time than most other antibiotics.

Indeed, the apparent universal sensitivity of staphylococci to neomycin has stimulated its use in the anterior nares of newborn infants and hospital personnel as a prophylactic measure (Rountree et al. 1956, Weinstein 1959). The spread and persistence of neomycin-resistant staphylococci in the Minneapolis General Hospital show, however, that *Staph. aureus* can adapt to this antibiotic as effectively as to others. Hence the use of this highly effective bactericidal antibiotic for prophylaxis, or for the treatment of insignificant surface infection, may be ill advised.

Summary

In a hospital study all cultures of coagulase-positive staphylococci have been tested for sensitivity to nine antibiotics, including neomycin, since 1955.

Until 1959, neomycin-resistant staphylococci were not found. In that year, however, they were cultured from 144 patients, and resistance to neomycin was found in 20·8% of 1248 cultures of coagulase-positive staphylococci. Among these strains of staphylococci, there was complete cross-resistance between neomycin and kanamycin.

Since staphylococci are evidently capable of acquiring resistance to neomycin, this valuable bactericide should be reserved for cases in which it is really needed. Its use for prophylaxis or in the treatment of unimportant surface infections appears inadvisable.

We gratefully acknowledge the cooperation and assistance of Dr. H. Dawes Miller, Dr. Claude R. Hitchcock, and Dr. Richard B. Raile at Minneapolis General Hospital, and Dr. Wesley W. Spink at the University of Minnesota Hospitals. We wish to thank Dr. Lewis W. Wannamaker for advice in preparation of the manuscript.

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THE CHROMOSOME COMPLEMENT IN TRUE HERMAPHRODITISM

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ABNORMALITIES of the chromosome sex-determining mechanism in man have long been considered a possible cause of human intersexuality (Painter 1923). It is, however, only with the recent advances in cytological technique that this hypothesis could be tested satisfactorily.

In an effort to learn more about the specific role of the sex chromosomes in sex determination, we have examined the chromosome complements in several disorders of human sexual differentiation. One of the most interesting, though possibly the rarest, is true hermaphroditism, in which both male and female gonads differentiate in the same individual. During the past year we have studied two true hermaphrodites, one with testis and ovary, the other with ovotestis and ovary.

Case-histories

Case 1 (previously reported by Goodwin et al. 1954).—The patient, a healthy Negro, was brought up as a boy. He was born in 1933 at which time his mother was 17 years old and his father 16. He was noted to have perineal hypospadias, a bifid scrotum, and an undescended left testis. At puberty the breasts began to enlarge, and it was observed that the right descended testis was small. Laparotomy revealed an immature uterus, a fallopian tube, and a normal left ovary; these were removed. A vas deferens emerged from the right internal inguinal ring and joined a rudimentary prostate. Histological examination of the ovary showed germinal follicles and normal ovarian stroma. A testicular biopsy specimen showed Leydig-cell hyperplasia, tubular hyalinisation, and germinal aplasia suggestive of chromatin-positive Klinefelter's syndrome (Ferguson-Smith et al. 1957). The patient is now married, and although childless gives a normal marital history. Axillary, pubic, and facial hair is within normal masculine limits and the gynæcomastia remains unchanged. Both buccal smear and review of previous histological material demonstrated a chromatin-positive pattern with single sex chromatin bodies. [J. H. H. no. 448002.]

Case 2.—The patient was born in 1945 when his mother was 24 and his father 25. He was brought up as a boy, although the diagnosis of sex was uncertain at birth owing to ambiguity of the external genitalia. There was a bifid scrotum containing a testis on the right side only, and a hypospadic phallus with perineal urethra and separate rudimentary vaginal orifice. Internal genitalia comprised a normal left ovary and fallopian tube, no true uterus, and a right vas deferens. The tube and ovary were removed in infancy. At puberty he developed striking enlargement of the breasts, together with deepening voice, facial acne, penile erections, and nocturnal emissions. Exploration of the right scrotal sac revealed a small ovotestis. Histological examination of this gonad reveals Leydig-cell hyperplasia and poorly developed seminiferous tubules, some containing a few spermatogonia. An area at the superior pole is composed of typical ovarian stroma, though no ova are seen. Nuclear sex is chromatin-positive.

Method of Chromosome Analysis

Cells for chromosome analysis are obtained by using a short-term culture technique for bone-marrow based on the method of Ford et al. (1958).

Bone-marrow is removed by sternal puncture under local anæsthetic, and approximately 0·5–1·0 ml. of the specimen is dispersed into each of several sterile tubes containing 10 ml. of heparinised Ringer's solution (50 units heparin per ml.). After removal of Ringer's solution by gentle centrifugation, the cell deposit is resuspended in 3 ml. of the patient's own serum. This is transferred to sterile 2-ounce prescription bottles containing 5 ml. of cell-culture fluid (Difco N.C.T.C. 109) and these are incubated on their sides at 37°C. It is usually possible to obtain enough marrow for several preparations. The first bottle is incubated for 5–7 hours only. During the last 2 hours of this period, deacetylmethyl-colchicine ('Colcemide' Ciba) is added to a final strength of 2 μg. per ml. (This drug is thought to interfere with the formation of the mitotic spindle and so serves to arrest and accumulate cells in mitosis.) After incubation the cell culture is centrifuged and the cells resuspended in 10 ml. of 1·12% (hypotonic) aqueous sodium citrate for 20–30 minutes at 37°C. The hypotonic treatment distends the cells and disperses the chromosomes throughout each mitotic cell. The suspension is once again centrifuged and the supernatant replaced by two changes of 50% glacial acetic acid. The cells are fixed for 15 minutes and then resuspended in 2–3 drops of 2% lacto-aceto-orcein stain (Welshons and Russell 1959). Squash preparations are made from this cell-stain mixture. The remaining bottles are treated similarly on successive days.

We have found it useful to divide the marrow specimen in this way because each cell culture may show a different degree of mitotic activity and the peak of activity varies. Usually the 24-hour specimen is the most satisfactory with regard to frequency of mitotic cells.

The squash preparations are scanned microscopically and the cells selected for counting and analysis. Those in which the chromosomes are either poorly dispersed or widely scattered are rejected. Once a cell is considered suitable, its chromosome complement is counted and recorded. With the help of camera-lucida drawings and photographic prints at ×3000 magnification, the chromosomes of each cell are graded according to total length and centromere position into one of seven groups (table I). This method of analysis enables the maximum amount of information to be obtained from the largest possible number of cells without requiring pairing of each chromosome. The sex-chromosome constitution is obtained by determining the number of chromosomes of groups III and VII (see table I).

TABLE I—SYSTEM OF CHROMOSOME ANALYSIS

Group	Size and centromere position	Idiogram number	Normal total number
I	Largest, median/sub-median ..	1–3	6
II	Large, sub-median ..	4–6	6
III	Medium, sub-median ..	7–12 and X	13 (male) or 14 (female)
IV	Medium, sub-terminal ..	13–15	6
V	Small, sub-median ..	16 and 17	4
VI	Small, median	18–20	6
VII	Small, subterminal ..	21, 22 and Y	5 (male) or 4 (female)
		Total ..	46

TABLE II—RESULTS OF CHROMOSOME COUNTS IN BONE-MARROW CELLS

Case	Number of cells with a chromosome count of					Total cells counted
	44	45	46	47	48	
1	8	15	74	22	0	119
2	1	7	75	2	1	86

The Y is unique, and readily identified as the largest chromosome in group VII. The X chromosome cannot always be identified with certainty as the largest chromosome in group III, because the chromosomes in this group are all very similar.

Results

The results of the chromosome counts are recorded in table II. In both cases most of the cells have the normal basic diploid number of 46. Of these cells, nine in case 1 and sixteen in case 2 are especially suitable for critical analysis. They all contain 14 group-III chromosomes and 4 group-VII chromosomes, a finding consistent with an XX sex-chromosome constitution.

A remarkable feature of case 1 is the high proportion of cells containing 47 chromosomes. Eleven mitotic plates are suitable for analysis. The extra chromosome in each clearly belongs to group III although it is impossible to identify it with a specific chromosome pair (fig. 1). Only one of the fourteen cells in this case with a diploid number of 45 is suitable for critical analysis. The missing chromosome again belongs to group III but it is not possible to identify it more exactly. Fragmentation of the chromosomes can be excluded as a cause of the observed aneuploidy because no structural abnormalities of the chromosomes can be seen.

In case 2, three cells with 46 chromosomes show in addition a small chromosome fragment, similar in each cell and reminiscent of an isochromatid deletion (see fig. 2, " F "). The few cells in which a count lower than 46 is observed do not show consistently loss of the same chromosomes and must be regarded as abnormal or damaged cells.

In most of the cells in both cases where a complete analysis of all the groups is not possible, the chromosomes in groups I, IV, VI, and VII can be identified. In no cell from either case are there more than 4 chromosomes in group VII. No characteristic Y chromosome can be found in any of the preparations.

Discussion

The possibility that true hermaphroditism in man is associated with an abnormal complement of sex chromosomes, such as an XXY constitution, had been suggested (see for example Painter 1923) ever since the classical work of Bridges (1916) on non-disjunction of the sex chromosomes in Drosophila. The demonstration of a normal basic diploid number of 46 and an XX chromosome constitution in the two cases described here, together with the results from two similar cases recently reported (Hungerford et al. 1959, Harnden and Armstrong 1959), excludes this possibility at least in the cases studied to date. It does not, however, exclude the possibility that the condition arises from some other type of abnormality of the sex chromosomes which causes a disturbance in the normal balance between the genes determining sex. Present techniques of chromosome analysis are not yet sufficiently refined to detect such chromosome aberrations, which might arise as small deletions or translocations.

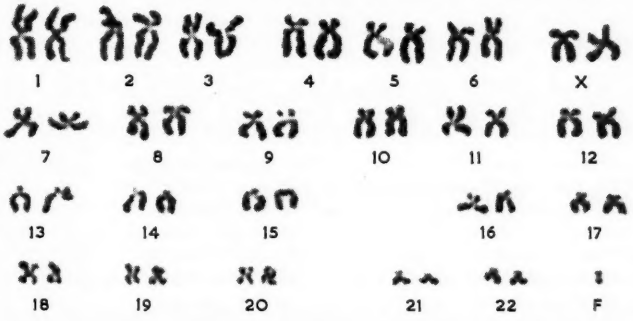

Fig. 2—Chromosomes from a bone-marrow cell in case 2 with an additional chromosomal fragment. (×1500 approx.)

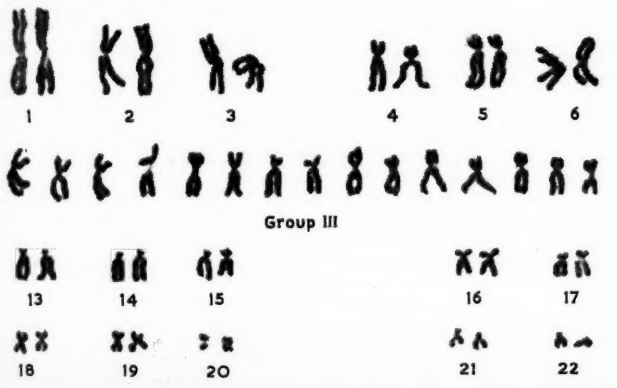

Fig. 1—Chromosomes from a bone-marrow cell in case 1 arranged according to table I. An extra chromosome is present in group III. (×1500 approx.)

It is possible that the high proportion of cells in case 1 which have one chromosome too many may be explained by the presence of three X chromosomes. This is suggested by the fact that in every cell of this type suitable for complete analysis the extra chromosome is in group III. This trisomic condition could be due to a high frequency of mitotic non-disjunction of the X chromosomes influenced by a chromosomal defect which may be associated with that producing hermaphroditism. This is the only indication of an abnormality in the X chromosomes. If mitotic non-disjunction of the X chromosomes were the explanation of the high frequency of cells with a count of 47, it would seem reasonable that an equal proportion of cells should contain only one X chromosome and have a total count of 45. The evidence for this is inconclusive. The only complete analysis available shows that the missing chromosome is in group III and might be an X.

The amount of aneuploidy found in case 1, on the other hand, may be of no significance with

regard to the cause of the hermaphroditism. It may represent a phenomenon confined to the bone-marrow, a site where the normal rate of cell-division is high and where abnormal mitoses in the maturing erythroblast might be expected. It is noteworthy that in the case of Hungerford et al. (1959) two cells from the leucocyte culture are interpreted as having 47 chromosomes.

There remains another explanation for the high incidence of cells with counts of 47 in case 1. It is possible that the patient is an XXX/XX mosaic of a type similar in ætiology to the case reported by Ford et al. (1959b) as an XXY/XX mosaic. They interpreted the findings as due to mitotic non-disjunction in an individual whose XXY constitution was derived from meiotic non-disjunction. However, the XXX individual reported by Jacobs, Baikie, et al. (1959) has no features in common with case 1 and has in addition a double complement of sex chromatin in a high proportion of intermitotic nuclei.

The recent discoveries that the sex-chromosome constitution is XXY in chromatin-positive Klinefelter's syndrome (Jacobs and Strong 1959), and is XO in chromatin-negative Turner's syndrome (Ford et al. 1959a), seemed to indicate that the Y chromosome is strongly male-determining in man (Ford et al. 1959b). In the house mouse exceptional female mice may have an XO pattern (Welshons et al. 1959), indicating that in these mammals the Y chromosome is necessary for male differentiation. This concept is contrary to previous theories of sex determination in mammals which have been based largely on studies in Drosophila, where sex is determined by a balance between male-determining genes carried on the autosomes and female-determining genes carried on the X chromosomes, the Y playing no significant part in this system. The absence of a normal Y chromosome in the four cases of true hermaphroditism studied to date is so far the only evidence against the hypothesis that the Y chromosome is essential to male determination in man. Support for alternative hypotheses is derived from the fact that the histological differentiation of the male gonad in the true hermaphrodite lacking a Y chromosome is as complete as that occurring in the XXY individual with chromatin-positive Klinefelter's syndrome.

An alternative explanation is that male-determining genes carried by the Y chromosome have been transferred in the true hermaphrodites to another chromosome by translocation. As the basic diploid number in these cases is 46, the presumed translocation must have taken place during meiosis resulting in an X gamete with the addition of masculinising genes from the Y chromosome. With the present cytological methods one cannot be certain that a small translocation has not taken place in the two cases reported here. There is at least no evidence of a large translocation involving most of the Y chromosome. The finding of an additional small chromosome fragment in three cells in case 2 is of interest in this respect, because this could be interpreted as the centromere-bearing remains of the Y chromosome which has taken part in a translocation and has persisted in a small proportion of cells.

In discussing the ætiology of true hermaphroditism, those cases reported by Grumbach and Barr (1958) to have male (chromatin-negative) nuclear sex must also be considered. Unfortunately there are no reports of chromosome analysis in these patients, but present views on the origin of the sex-chromatin suggest that they have only one X chromosome. In Grumbach and Barr's series 6 out of 25 were found to be chromatin-negative. No correlation was observed between the type of sex differentiation and the nuclear sex. This observation in itself suggests that there are several causative factors and that more than one karyotype may be associated with true hermaphroditism.

In the absence of an obvious chromosome anomaly as the cause of true hermaphroditism, other factors must be considered. We shall not discuss the embryological aspects except to emphasise that an abnormal stimulus, in order to produce unilateral male sex differentiation in a female fœtus, must exert its effect principally on one gonad and must operate on the undifferentiated gonadal anlage at a very early stage of gestation, almost certainly before seven weeks. It is difficult to see how the abnormal stimulus could be hormonal or be derived from the maternal environment, and there is in fact no evidence to support this in man. Another theory (Witschi et al. 1957) involves degradation of the fertilised egg and embryo, with specific damage to the developing and migrating germinal cells which are considered important in the initiation of differentiation of the appropriate gonad and thereafter the appropriate genital ducts.

Summary

Chromosome analyses are described in two cases of true hermaphroditism. The basic diploid number in each is 46 and the sex-chromosome constitution is interpreted as XX. In one patient 18·5% of cells had a chromosome count of 47. Despite the presence of a testis in one case and an ovotestis in the other, no Y chromosome was present. This finding is discussed in the light of modern views on the function of the Y chromosome in human sex determination.

Our thanks are due to Dr. John Money for referring case 1 and to Dr. W. J. Young for reading the manuscript.

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Addendum

Since the submission of this paper, a standard system of nomenclature for human chromosomes has been proposed (*Lancet*, 1960, i, 1063). This Denver system, which for the sake of uniformity should be generally adopted, differs from the one used above, in the numbering of chromosomes 16, 17, and 18. The corresponding numbers in our system are 18, 16, and 17.

" I would like to suggest . . . that it would be possible . . . to select a representative series of families throughout the country (say one per cent. of the total) and to obtain from the family doctor an inventory of permanent defects and of intercurrent illnesses over the preceding year for each member of each sample family. This information could be supplemented from the Medical Officer of Health and his medical and nursing staff in relation to medicosocial data, including that available from the school health service, the whole forming a comprehensive picture of the health and sickness experience of a sample sufficient and selective to reflect that of the population as a whole. Such surveys . . . would illustrate current problems of ill-health and form a growing and permanent record of disease which would eventually have a social and genetic value of the first importance."—Sir KENNETH COWAN, *The Climate of Health*; p. 33. (Edinburgh: Royal College of Physicians. 1960.)

CHROMOSOMAL CONSTITUTION AND NUCLEAR SEX OF A TRUE HERMAPHRODITE

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THE findings of nuclear dimorphism in human tissues of both sexes and the introduction of new techniques for the ascertainment of the chromosomal constitution have added new interest to the study of intersex patients (Moore and Barr 1953, Décourt et al. 1954, Nelson 1956, Tjio and Levan 1956, Jacobs and Strong 1959, Ford et al. 1959).

Fig. 1—The patient.

We report here the results of chromosomal counts and the determination of nuclear sex in a case of true hermaphroditism. Chromosomal study was performed according to the new technique developed by one of us (C. B.). Nuclear sex was studied in oral smears. (After acid hydrolysis, buffered toluidine-blue was used.)

Case-report

A " boy ", 14 years old, was admitted to the metabolic department complaining of excessive development of the mammary region. Micturition had never been of the male type, the external genitals being abnormal. He had always had good health. Physical development had been normal.

At the age of 13, a quick growth spurt, coinciding with the appearance of pubic and axillary hair, was noted. (Facial hair has not appeared hitherto.) At the same time, after an initial painful period, quick and excessive growth of the mammary glands was noted (fig. 1). The patient has three normal brothers and a normal sister. The mother is healthy. The father died when the patient was 3 years of age.

The patient's general condition was fair. Psychological study revealed a masculine personality with a few feminine traits. Height: 5 ft. 3 in. Weight: 88 lb. Span: 5 ft. 5 in. Pubis-heel measurement: 2 ft. 11 in. Pubis-head measurement: 2 ft. 4 in. Relation of superior segment to inferior segment 1 : 1·2. Biacromial diameter 1 ft. 2 in. Bitrochanteric diameter 10 in.

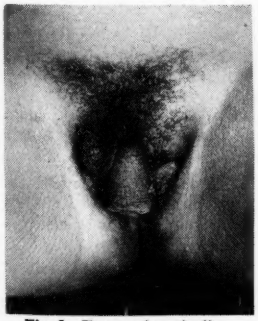

Fig. 2—External genitalia.

Clinical examination revealed no abnormality except for the external genitals; pubic hair in fair quantity, long and thick, in female distribution; axillary hair scarce and long. Penis 6 cm. long, without the urethral meatus, bending ventrally through a ligament connecting the ventral surface to the perineum (fig. 2). Thus the scrotum appeared to be bifid; a depression with a small meatus was visible in the midline. No testes could be felt in the labioscrotal folds. A small mass, about 1 in. in diameter, was felt in the right groin, giving the impression of being elastic. In the left groin no evidence of a testicle was found.

The connection between the perineal meatus and the urogenital sinus was shown by urethroscopic examination. Urethrocystography indicated a connection between the urogenital sinus and the vagina, uterus, and a left oviduct. There was also a connection with the urethra and the bladder.

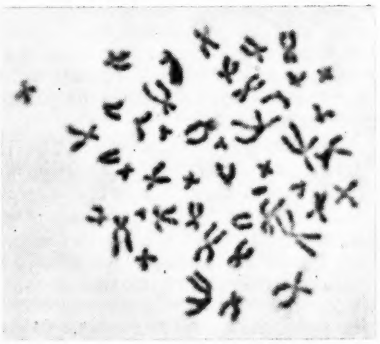

Fig. 3—46 chromosomes, including 4 small acrocentric chromosomes.

A small uterus (2–3 cm. long), a left ovary, a round ligament, and a left fallopian tube were revealed by laparoscopy, and these findings were confirmed by subsequent laparotomy. On the right side a round ligament was present, but no ovary or adnexa were seen. At the right inguinal canal an elongated mass, similar to an almond, was noted: ovarian tissue was present in two-thirds of it (subepithelial follicles were visible); the elasticity of the remaining third suggested testicular tissue. Over the ovarian pole an oviduct with a pavilion at its free end was noted. Connected by loose connective tissue to the fallopian tube, and parallel to it, was an apparently normal vas deferens. No epididymis was felt.

Biopsy of the inguinal mass showed both ovarian and testicular tissue. In the ovary, follicles in different maturation stages were found, with a single large mature one; atresic follicles were also present. There was no corpus luteum. In the testicle, the tubules had the appearance found in the ectopic gonad. Urinary œstrogens (Allen-Doisy method): more than 8 rat units per 24 hours; 17-ketosteroids (Dreckter method): 3·8 mg. per 24 hours; 17-hydroxycorticosteroids (Porter-Silber method): 3·3 mg. per 24 hours. The bone age and texture were normal. The sex chromatin was found to be female in material obtained from the mucosa of both the left and the right cheek. Basal temperature charts showed lack of ovulation. Vaginal cytology: no evidence of œstrogenic activity. Pregnanediol estimations: inconclusive. The bone-marrow specimens, for studying the chromosomal constitution, were obtained by sternal puncture, after intravenous adminis-

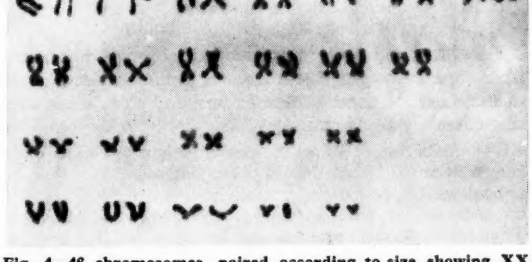

Fig. 4—46 chromosomes, paired according to size, showing XX constitution.

tration of colchicine, according to Bottura's method. In the 25 cells examined, a constant number of 46 chromosomes was found. In 16 cells, in which the chromosomes were particularly well spread, four small acrocentric chromosomes could be perfectly identified (fig. 3). After pairing, the chromosomal constitution was found to be XX, indicating female sex (fig. 4).

Discussion

Harnden and Armstrong (1959) have published a case of true hermophroditism showing the same chromosomal constitution but with a more definite masculine appearance (male hair distribution, no breast development). Hungerford et al. (1959) published a case with male phenotype with testis and ovotestis, and the sex chromosomes were interpreted as XX.

Considering the attempts which are being made at a pathogenic interpretation of intersex, all reports of such cases are of interest. In view of the special features of the present case, we hope that this report will prove a useful contribution.

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TRISOMIC CONDITION OF A LARGE CHROMOSOME IN A WOMAN WITH MONGOLOID TRAITS

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HAVING noted in a young woman atypical mongoloid traits, one of us (E. P.) thought it would be interesting to ascertain her chromosome pattern and compare it with that of a typical mongol.

The patient, aged 19, is 167 cm. in height and weighs 49·5 kg. Habitus longilineus-asthenicus. Palpebral fissures slightly slant upwards at the outer corner of the eyes. Thyroid: moderately enlarged and firm (basal metabolic rate −12, −6); ^{131}I intake increased (71% in 24 hours) with delayed excretion (30% in 24 hours) and conversion index increased (73%). Menstruation rather frequent and abundant. External genitals and breast slightly underdeveloped with hypoplastic uterus. Pubic hair normal. Vaginal smear (Papanicolaou): good œstral modification. Urinary excretion of 17-ketosteroids 9·04 mg. in 24 hours. Urinary excretion of gonadotrophin <29 mouse units. No mongoloid palmar patterns; no cataract. Psychological examination (psychological institute, Catholic University of Milan): low global intellectual efficiency; intelligence quotient 70 (Wechsler-Bellevue test). Electroencephalogram normal. Colour-vision normal. Barr chromatin body (Prof. M. Preto and Dr. G. Roncoroni, histological institute, University of Milan): as for female. The proportion of cells containing chromatin bodies (57%) is greater than that found in buccal smears of normal women and some of the nuclei (8% certainly, 8% doubtfully) contain two chromatin bodies.

Fragments of fascia lata, one from this "paramongol" and one from a typical mongol, were sent for investigation at the institute of genetics, University of Pavia.

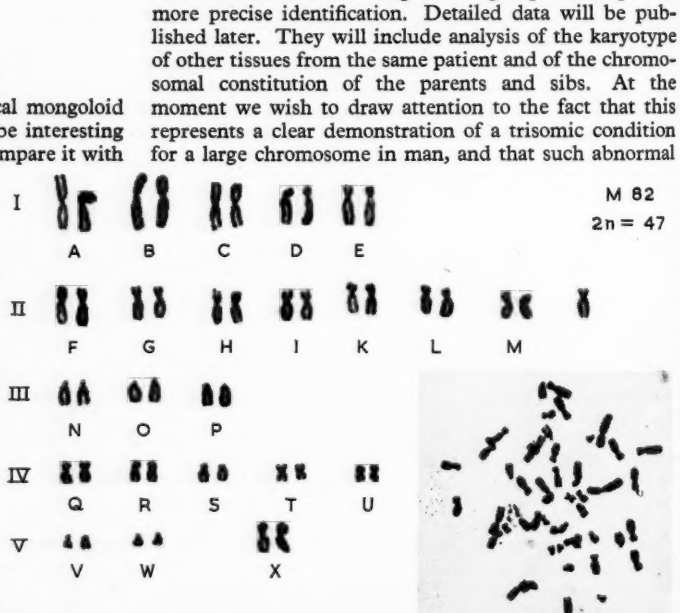
These fragments were cultured in plasma clot on coverslips placed in petri dishes. For growing the cells Puck's medium for fibroblasts was used and the cultures were incubated in a CO_2 atmosphere. Ten days later explantation preparations were made by a method which combines the technique of Tjio and Puck (1958) and Lejeune, Gauthier, and Turpin (1959). To avoid distortion of the normal appearance of the chromosomes, colchicine was not used.

In the tissues of the typical mongol we found the additional small chromosome characteristic of mongolism (Lejeune, Gauthier, and Turpin 1959). In the "paramongol", too, the chromosome counts showed a modal diploid number of 47:

Number of chromosomes	42	43	44	45	46	47	48 . . . 94
Number of cells	1	..	2	2	2	24	.. 2

But in this patient the extra chromosome was of medium size. Arrangement of chromosomes in pairs (see figure), which we performed in ten metaphase plates, clearly demonstrates that this chromosome can be assigned to group II of our classification (Chiarelli et al. 1959) or to group III of the classification proposed by Levan and Hsu (1959).

Since the X chromosomes are similar in length and arm ratio to some members of the group involved, the possibility was also considered that the 47th chromosome might be an extra X. Data so far collected, however, make it likely that the additional chromosome is an autosome, possibly homologous to the pair K or L of our classification. Careful morphometric analysis of the chromosomes which belong to our group II will permit more precise identification. Detailed data will be published later. They will include analysis of the karyotype of other tissues from the same patient and of the chromosomal constitution of the parents and sibs. At the moment we wish to draw attention to the fact that this represents a clear demonstration of a trisomic condition for a large chromosome in man, and that such abnormal



Mitotic metaphase and arrangement of chromosomes in pairs.

karyotype is evidently compatible with normal development.

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ZOLLINGER-ELLISON SYNDROME WITH DIARRHŒA AND MALABSORPTION

OBSERVATIONS ON A PATIENT BEFORE AND AFTER PANCREATIC ISLET-CELL TUMOUR REMOVAL WITHOUT RESORT TO GASTRIC SURGERY

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IN 1955 Zollinger and Ellison gave an account of two patients in whom they had observed pancreatic islet-cell tumours with primary jejunal ulceration associated with gastric hypersecretion, and they postulated that the tumours secreted some substance capable of exciting gastric secretion. Since then more than thirty-five cases of this nature have been published, and details of at least seventy-five have been tabulated in a register (Zollinger and Elliott 1959). It has still not been established, however, that the pancreatic tumours really do influence gastric secretion, and, if so, by what mechanism. To date there have been no reports of patients in whom no gastric surgery has been performed but in whom gastric secretory studies have been carried out before and after simple removal of the tumour.

In the following case the sole operative procedure was removal of a pancreatic islet-cell tumour. Gastric secretory capacity and fæcal fat excretion were studied before and after operation. The results suggested a close relation between the excessive gastric secretion and the tumour.

Case-report

A man, aged 55, a weighbridge operator, was admitted to hospital in May, 1959, for investigation of diarrhœa which had been present for 8 years, gradually increasing in severity. Symptomatic treatment had proved of no value. For 2 years he had had attacks of retrosternal pain, occurring particularly when lying flat, unrelated to meals, but relieved by alkali. For 18 months he had had episodic dyspepsia and attacks of vomiting and there was radiological evidence of a duodenal ulcer. However, he made light of his dyspepsia and complained mainly of diarrhœa, being much distressed by frequent nocturnal incontinence. His appetite was good but his weight had fallen from 15 st. (210 lb.) to 11½ st. (161 lb.) in 2 years. He had no soreness of the tongue or mouth. He had never had symptoms suggestive of hypoglycæmic attacks.

He was a well-nourished man with no abnormal physical signs except some finger clubbing. Rectal examination normal. Blood-pressure 140/80 mm. Hg. Hæmoglobin 110% (16·3 g. per 100 ml.). Barium meal showed a persistent deformity of the apex of the duodenal cap. Test meal: high acid curve. Stool examination: excessive fat (15 g. daily).

A tentative diagnosis of idiopathic steatorrhœa was made and treatment with a gluten-free diet instituted. After 2 months without improvement of his diarrhœa or nutritional state, pancreatin was included with meals. After a further month, it was concluded that neither treatment was altering his condition and he was transferred to the medical unit, Queen Elizabeth Hospital, for further study of his steatorrhœa.

Investigations

His hæmoglobin had now fallen slightly to 98% (14·3 g.). No macrocytes were seen in a peripheral blood-smear. White blood-cells 12,000 per c.mm. (differential count normal). Erythrocyte-sedimentation rate 10 mm. in one hour (Wintrobe); blood-group, A; Rh-positive. Oral glucose-tolerance test showed a high lag curve, but an intraduodenal glucose tolerance test was normal. Liver-function tests normal; serum-albumin 4·4 g., serum-globulin 3·0 g., per 100 ml.; cholesterol, free 40 mg., ester 185 mg. per 100 ml.; serum sodium, potassium, and chlorine normal, calcium 9·8 mg., phosphorus 1·7 mg. per 100 ml.; alkaline phosphatase, 3·4 units per 100 ml. (Jenner and Kay); van den Bergh direct and indirect negative. Wassermann and Kahn reactions negative.

The stools were again found to contain an excess of fat (15–20 g. daily on a 70 g. fat intake). Microscopically, the fat appeared mainly as soaps; no excess of meat fibres or starch. Stool culture negative for organisms of the salmonella and

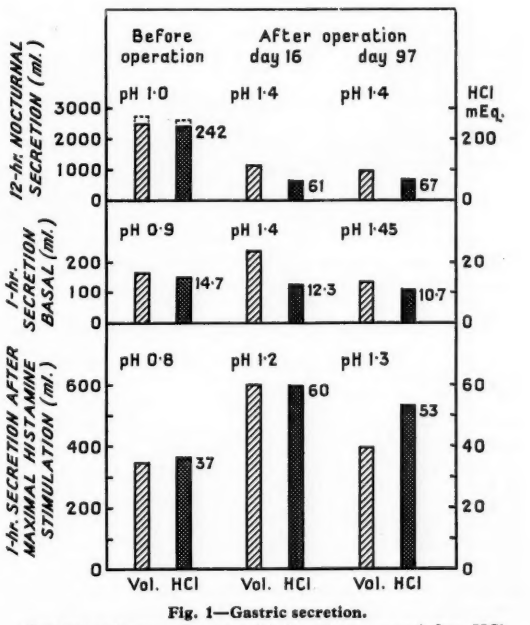

Fig. 1—Gastric secretion.

Hatched columns=volume; black columns=total free HCl.

Before operation:

Nocturnal secretion showed a gross excess over normal values both in volume and total free HCl. (Normal values: volume 148–1188 ml. [average 581 ml.]; total free HCl 0·5–94·0 mEq. [average 18·2 mEq.]. From studies in 33 subjects by Levin et al. 1948). Basal secretion was high but a further increase took place after histamine.

After operation:

Nocturnal secretion was greatly reduced. Basal secretion was slightly less but there was an enhanced response to histamine. N.B.—Dehydration was particularly evident clinically after the aspiration of 2·5 litres of fluid in the preoperative nocturnal secretion test. This may have modified the response to the basal and histamine tests which followed immediately.

shigella groups; positive for *Candida albicans*. Occult blood positive. Pancreatic lipase and trypsin activity in duodenal juice normal.

The examination for pancreatic enzymes was performed by passing a radio-opaque tube into the second and third parts of the duodenum and aspirating unstimulated juice with the patient lying on his right side. After some time, three satisfactory samples of clear yellow alkaline juice were obtained, approximately 5 ml. each. During the intubation, sampling of alkaline bilestained juice was almost continuously interrupted by the aspiration of fairly large samples of acid gastric juice (5–10 ml., pH 1·0–1·5); the amounts were sufficiently copious to suggest that the tube had been withdrawn into the stomach and the patient was therefore re-screened, but the tube undoubtedly lay in the second and third parts of the duodenum. This persistent finding was so unusual that it suggested an excess of gastric secretion requiring further examination.

Œsophagoscopy showed œsophagitis. Barium meals showed no abnormalities of œsophagus or stomach and no œsophageal reflux or hiatus hernia; the duodenal cap again appeared deformed. Two examinations of the small intestine were carried out: (1) ordinary suspension of barium sulphate showed gross flocculation beginning in the jejunum; (2) non-flocculating ('Raybar', Damancy) showed a wide dilated small intestine with coarsening of the mucosal folds and lack of secondary arborisations (ladder pattern). With both meals the small intestine showed changes seen characteristically in idiopathic steatorrhœa or sprue. No evidence of jejunal ulceraton was seen on careful examination during the raybar meal. Barium enema was normal.

Special Studies

Gastric secretion: 12-hour nocturnal gastric secretion was collected with continuous suction by pump from 8 P.M. to 8 A.M. through a radio-opaque Ryle's tube which had previously been screened into position along the greater curve of the stomach with the tip near the pyloric canal. Immediately after this, an hour's basal (unstimulated) secretion was aspirated. A further hour's secretion was then collected after maximal histamine stimulation (0·04 mg. histamine base per kg. body-weight) under cover of an anti-histamine injected 45 minutes beforehand (Kay 1953). The results (fig. 1) showed that there was an enormous nocturnal secretion of HCl (246 mEq. in 11 hours actual). Fæcal fat and volume were measured daily and the results indicated that both were excessive through the preoperative period (fig. 2).

Diagnosis

On the basis of the watery type of diarrhœa, steatorrhœa, peptic ulceration, œsophagitis, and grossly excessive gastric secretion, a diagnosis of Zollinger-Ellison syndrome was made and laparotomy performed.

Operation

The colon appeared smooth on its serosal surface and slightly thicker than normal. Two small pearly white nodes about the size of a lentil were found on the under surface of the liver and one was excised for microscopic examination. The duodenum was thickened and an inflammatory reaction and petechial hæmorrhages indicative of ulceration within were seen anteriorly; on opening the lesser sac the site a of second ulcer was found. The stomach, the rest of the small intestine, and the spleen were normal. The body and tail of the pancreas were normal on palpation, but a nodule the size of a cherry was felt arising from the left side of the head of the pancreas. This tumour was removed and on examination about three-fifths appeared to have been dissected from within the pancreas. A frozen section showed an adenoma. The question of malignancy and the outlook in total pancreatectomy were discussed; and, when no enlarged glands or tumiform lesions were discovered after a thorough search, it was felt possible that this might be a purely local lesion. It was therefore decided that local excision was justifiable and that vagotomy and gastrectomy for duodenal ulcer were not called for.

The patient made an uneventful recovery except for a small pulmonary infarct on the 6th postoperative day, for which he received anticoagulants for a while. After operation he had no further diarrhœa, vomiting, or retrosternal or epigastric pain. In fact, from the day of operation, he was completely free of his original symptoms and rapidly gained weight (fig. 2).

Postoperative Repetition of Tests

Gastric secretion tests were repeated on the 16th and 97th postoperative days and showed that

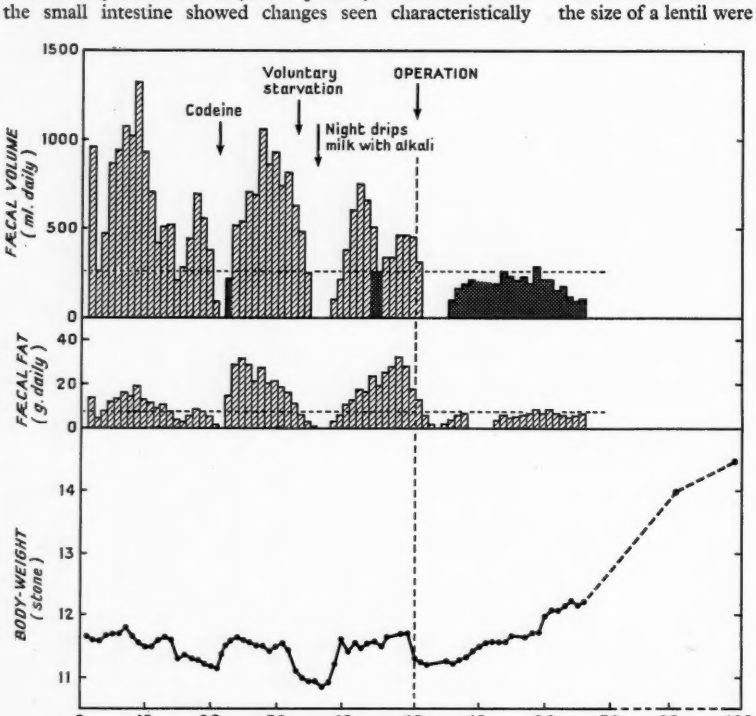

Fig. 2—Fæcal volume, fat and body-weight.

Before operation:

The fæcal volume and fat excretion were greater than normal. The black areas represent formed stools and the hatched areas diarrhœa. It will be seen that the favourable effect of codeine and alkalis on the diarrhœa were limited to 2–3 days. Aspiration of nocturnal gastric secretion caused the diarrhœa to cease for one day.

After operation:

Fæcal fat and volume reverted to normal values. The stools were formed. Body-weight increased rapidly.

Fat intake.—For the first 37 days, the fat intake was 70 g. per day, thereafter 100 g. until operation. Within 10 days of the operation he was taking an ordinary diet containing about 80 g. fat daily.

secretion had diminished considerably from 246 mEq. in 11 hours before operation to 63 and 67 mEq. in 12 hours after (fig. 1).

The Tumours

The *pancreatic tumour* was about the size and colour of a cherry, and on incision, the cut surface (fleshy in nature) was also a cherry red. Immediately after removal it was divided into two unequal pieces. One-third was retained in Birmingham for histological examination and two-thirds were placed in a vacuum flask at −70°C and despatched to Dr. W. Sircus, of the gastrointestinal unit, Western Royal Infirmary, Edinburgh, for special studies (Gregory, Tracy, French, and Sircus 1960). Histologically, section showed that it was an islet-cell tumour infiltrating a lymph-gland. The tumour cells were well differentiated, forming a regular trabecular pattern. There was also considerable vascularity, and groups of tumour cells were seen within several of the vascular channels. The tumour was regarded by the pathologist as malignant.

Tissue was fixed in both 10% formol saline and Helly's fixative for granule stains. In formalin-fixed tissue both red and blue staining was noted but no convincing granularity was observed. In Helly's fixative, definite granularity was seen in many of the cells, especially in some large cells which stained dark purple with granules (Gomori's chrome alum hæmatoxylin, which stains beta-cells deep blue and alpha-cells bright red). With Gomori's aldehyde fuchsin the results were equivocal, but a fair number of beta-cells were present in the tumour.

The *liver nodule* on section consisted of irregular duct-like channels lined by low cuboidal flattened epithelium, the channels being separated by a fibrous stroma. The nodule appeared to be a non-malignant malformation of bileducts (hamartoma) and bore no resemblance to the pancreatic tumour.

Follow-up

The patient has been kept under observation for a further 6 months, is symptom-free, and has gained a further 10 lb. in weight. Although at operation all discernible tumour was removed, a regular check of the patient's condition is clearly indicated, including studies of gastric secretion at intervals.

Discussion

In 1948 Poth et al. suggested that some element in the pancreas might be responsible for peptic ulceration. This concept was based on the observations of Elman and Hartman (1931) that (in dogs) complete diversion of the external pancreatic secretions from the duodenum nearly always gave rise to duodenal ulceration, whereas total pancreatectomy rarely did so (Dragstedt et al. 1939), though both operations abolished external pancreatic secretion. They suspected islet tissue. When Zollinger and Ellison (1955) reported their two cases of islet-cell adenoma of the non-insulin-secreting type associated with primary jejunal ulceration and gastric hypersecretion, they reviewed a further seven cases in which similar tumours had been associated with duodenal or jejunal ulceration, and they regarded this as a syndrome in support of Poth's concept.

Retrospective study of the case-records of this type shows quite frequent complaints of diarrhœa, sometimes for many years before symptoms of peptic ulceration appeared; but the presence of the tumour has remained unsuspected until recurrent peptic ulceration led to major gastric operations or the patient came to necropsy. Consequently, though it has been suggested that the tumour is in some way responsible for the hypersecretion of the stomach, hitherto the only observations to determine the influence of tumour removal upon gastric secretion are those in two patients in whom near-total gastrectomy had already been carried out and only a small gastric remnant was left to study (Oberhelman et al. 1958, Zollinger and McPherson 1958). In their original study Zollinger and Ellison thought that glucagon secreted by the alpha-cells was responsible for the hypersecretion, but it is now known that injection of glucagon depresses gastric secretory activity (Dreiling and Janowitz 1959, Clarke et al. 1960).

The case we record shows for the first time that removal of a pancreatic islet-cell tumour may reduce excessive acid secretion in the intact stomach. Though the histological nature of the tumour cells was not clear, the equivocal staining and the absence of hypoglycæmic symptoms suggests that the bulk of the tumour was not of a beta-cell type. The simultaneous disappearance of diarrhœa and steatorrhœa after operation strongly supports the opinion of Summerskill (1959) that they are caused by grossly excessive gastric acid. Though limited to one case, our observations are in line with Zollinger and Ellison's contention that these tumours actually stimulate excessive gastric secretion. Experimentally, extracts of the tumour have now been found to stimulate secretion in gastric pouches in dogs (Gregory, Tracy, French, and Sircus 1960).

If these observations are confirmed in other patients with tumours of a similar type, they may have an important bearing on peptic ulceration in general. Whereas nocturnal secretion in gastric-ulcer patients is within normal limits, duodenal-ulcer patients secrete large volumes of highly acid gastric juice when there is no known stimulus to the gastric secretory mechanism. The present findings may be a key to the mechanisms of the duodenal ulcer.

Diarrhœa and Steatorrhœa

Diarrhœa as an early and comparatively frequent symptom has not had the attention it deserves. Zollinger and Elliott (1959) in a recent review give it only brief mention. However, Verner and Morrison (1958) were impressed by it in their two patients, and in reviewing twenty-seven other patients with non-beta-cell tumours they noted that a refractory watery diarrhœa was prominent in seven. In five of these the diarrhœa preceded by many years the symptoms of peptic ulcer—an observation also made in several recent reports. Both patients of Verner and Morrison died with hypokalæmia which resulted directly from the chronic severe diarrhœa; and these authors remark that no satisfactory clinical explanation of the diarrhœa was found either in their cases or in the other seven reviewed. In neither of their patients was duodenal or jejunal ulceration demonstrable at necropsy. In at least one instance longstanding diarrhœa has disappeared after the removal of an alpha-cell adenoma (Brown et al. 1950). Thus hypersecretion, diarrhœa, and tumour may be present for years before peptic ulceration takes place (as in the patient of Donaldson et al. 1957) and the diarrhœa may prove fatal in the absence of ulceration. To recognise that islet-cell tumours of this nature give rise to diarrhœa in a high proportion of cases is clearly important; for in suitable cases early removal of the tumour will not only cure the diarrhœa but also prevent the disastrous sequelæ of operations for peptic ulceration in this condition.

Attention was first drawn to the steatorrhœa by Maynard and Point (1958), and it can be a striking feature (Summerskill 1959). In patients with diarrhœa it may be much commoner than has been supposed.

Several mechanisms have been invoked to explain the steatorrhœa and diarrhœa:

1. The pancreas may be largely destroyed or the ducts blocked by tumour.

2. Hypersecretion may occur in the small and large bowels as well as in the stomach.

3. The large volume of HCl passing into the small intestine may be incompletely neutralised by pancreatic bicarbonate, and the low pH impair emulsification and lipolysis. Not only is lipase inactivated at a low pH, but it may be rapidly destroyed in the presence of HCl and pepsin.

Summerskill (1959) showed that the pH in the lower duodenum and upper jejunum was between 1·0 and 2·0 for most of the 24 hours, and his finding strongly favours the third explanation.

In our patient, the copious flow of gastric juice into the duodenum made it difficult to aspirate any but very small amounts of alkaline juice; and it seemed likely that, in him also, the pH of the upper small intestine was abnormally low for much of the digestive period. The disappearance of diarrhœa and steatorrhœa when gastric secretion diminished after operation tends to confirm the hypothesis that they were both due to the acid conditions in the small intestine.

Summary

In a patient with an 8-year history of intractable diarrhœa and a 2-year history of symptoms of peptic ulceration a diagnosis of Zollinger-Ellison syndrome was made. Investigation showed gross gastric hypersecretion and steatorrhœa. At operation a tumour containing islet (non-beta) cells was removed from the pancreas. After operation there was no further diarrhœa and no steatorrhœa. The disappearance of symptoms coincided with a large decrease in the rate of secretion of gastric juice and acid.

These results support the hypothesis that certain pancreatic islet cells can stimulate gastric secretion.

We are indebted to Dr. J. B. W. Halley for the histological examinations, to Prof. W. Melville Arnott for his stimulating advice, and to Miss Vanessa Cotton for biochemical assistance.

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Preliminary Communication

DETECTION OF VENOUS THROMBOSIS WITH ^{131}I-LABELLED FIBRINOGEN IN THE RABBIT

POSTOPERATIVE venous thrombosis is still a serious and common risk although treatment with anticoagulants may prevent fatal complications. Diagnosis depends on clinical manifestations, and by the time symptoms or signs are present the thrombosis may be extensive; hence treatment is begun late. In this study ^{131}I-labelled rabbit fibrinogen was used to show whether an artificially induced thrombus in the rabbit's leg could be identified by means of an external radiation detector.

METHODS

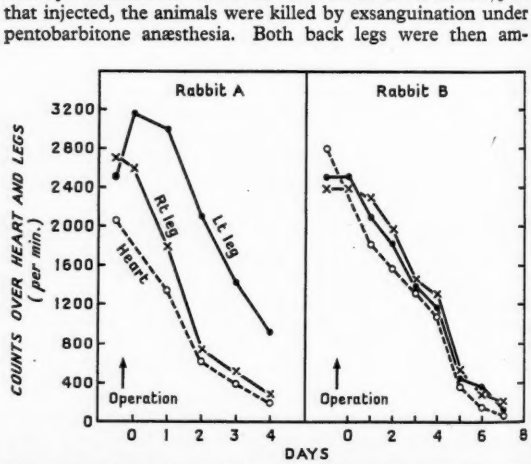
Fibrinogen was isolated from rabbit blood taken by cardiac puncture with the animal heparinised by the method of Biggs and Macfarlane.[1] This fibrinogen was iodinated with ^{131}I using a modification of the method of McFarlane [2] in which various volumes of *N* ammonium hydroxide replaced the alkaline glycine buffers. The fibrinogen was labelled to a level of 3–10 μC per mg. protein, and at less than 1 atom of iodine per protein molecule. In the final labelled material less than 2% of the radioactivity was in the form of free iodide. Using the radioactivity as an index, about 75% of the labelled protein was clottable with thrombin.

10–25 μC of the labelled fibrinogen solution, containing 2–5 mg. protein, was injected intravenously into eleven rabbits through the ear vein. The rabbits were then anæsthetised with intraperitoneal pentobarbitone sodium ('Nembutal'), and strapped to a board. A scintillation counter, fitted with a 1-inch sodium-iodide crystal and a collimator of 6·5 cm. aperture and 6·5 cm. deep, was placed over the back legs between knee and ankle, and also over the heart. Sufficient counts were made to ensure that the random distribution error was less than $\pm$2%.

Operations on seven of the eleven rabbits produced thrombosis of the left long-saphenous vein by the following methods: in two rabbits the vein and its major communications were ligated; in three a single ligature was combined with retrograde injection of sclerosing agent (5% ethanolamine oleate *B.P.*); and in two coagulation was achieved by diathermy.

Of the remaining four rabbits, two were controls and had no operation, and two had a mock operation—i.e., the left long-saphenous vein was isolated through a skin incision but not ligated, and the skin was then closed using nylon sutures. No operation was performed on the right leg of any rabbit, which thus acted as a control for the left leg.

The counts over the two back legs and the heart were measured within 30 minutes of operation, and then at daily intervals for up to 10 days, the rabbits being anæsthetised each day and strapped to the board in the same position to ensure constant resting conditions. All the counts were corrected for radioactive decay back to the day of injection. When the radioactivity contained in the rabbits had fallen to about 20% of that injected, the animals were killed by exsanguination under pentobarbitone anæsthesia. Both back legs were then am-



Radioactivity in the legs and heart of a rabbit with thrombosis (A) and of a control (B).

1. Biggs, R., Macfarlane, R. G. Human Blood Coagulation and Its Disorders; p. 389. Oxford, 1957.
2. McFarlane, A. S. *Nature, Lond.* 1958, **182**, 53.

putated through the knee and ankle joints, and the radioactivity contained in the isolated legs was determined by counting in the same position as in the live animal. The legs were then dissected, and the tissues were divided into four groups thus: (1) skin; (2) long-saphenous vein; (3) muscles, tendons, deep vessels, &c.; and (4) bone. These tissues were weighed, and their radioactivity was determined with a well-type scintillation counter. The counts per gramme of tissue were calculated.

Evidence of the extent of thrombosis was determined by serial histological section of each vein—half transversely and half longitudinally. Autoradiographs of some of these sections were made to demonstrate the site of the radioactivity.

RESULTS

Typical data from two rabbits are shown in the figure. In rabbit A thrombosis was caused by ligature and the injection of sclerosing agent, whilst rabbit B only had a mock operation. The heart and right-leg counts show the rate of disappearance of ^{131}I from the circulation.

The difference between the counts in the two legs is considerable in the rabbit with thrombosis compared with that in the control animal. Very similar results were obtained in the two other rabbits in which thrombosis was caused by sclerosing agent. The difference between the thrombotic and non-thrombotic legs was less when the thrombi were caused by simple ligature or diathermy, because these methods caused much less thrombotic reaction. The postmortem tissue-counts (see table) also

RADIOACTIVITY (COUNTS PER MIN. PER G. TISSUE) IN A RABBIT WITH THROMBOSIS (A), AND IN A CONTROL (B)

Tissue	Rabbit A		Rabbit B	
	Left leg	Right leg	Left leg	Right leg
Skin	360	191	849	420
Vein	8225	97	409	300
Muscle ..	39	75	114	130
Bone	0	0	0	0

indicate that nearly all the radioactivity was contained in the thrombosed left long-saphenous vein, whilst autoradiographs confirmed that the thrombus contained the radioactivity.

DISCUSSION

As McFarlane has shown,[3] carefully iodinated proteins from an animal species are not destroyed by the same species more rapidly than unlabelled proteins; hence radioactively labelled fibrinogen should be used at the same rate and for the same purposes as unlabelled fibrinogen.

The evidence presented here shows that when ^{131}I-labelled fibrinogen is in circulation at the time a thrombus is formed, some of it is incorporated in the clot. This radioactivity can be identified by an external radiation detector as well as by histological and autoradiographic techniques. A method is thus available for measuring the rate of thrombus formation.

A study using these methods but with variations in the time of injection of the labelled fibrinogen relative to the time when thrombosis is caused, and studies in animals receiving anticoagulants, either by mouth or intravenously, may have useful clinical applications in the diagnosis of postoperative thrombosis in man.

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3. McFarlane, A. S. *Biochem. J.* 1956, **62**, 135.

Medical Societies

HEBERDEN SOCIETY

Treatment of Rheumatoid Arthritis

A MEETING of this society was held in Manchester on July 1–2, with Dr. F. DUDLEY HART, the president, in the chair. The papers included three reports of controlled therapeutic trials in rheumatoid arthritis.

Gold

Describing the Empire Rheumatism Council's clinical trial of gold therapy, Dr. DUDLEY HART said that two hundred patients from 24 centres were divided into two equal and comparable groups. One group received 20 weekly injections of sodium aurothiomalate to a total of 1 gramme, and the other group, acting as controls, received $^{1}/_{100,000}$ of this amount to a total of 0·01 mg. in 20 weeks. Patients were allocated to their groups by the statistician, Dr. Lewis-Faning, and the injection solutions were then supplied to the centre, so that assessor and patient remained ignorant of the dosage being given. Assessments were made at 1, 3, 6, 12, and 18 months, in respect of functional capacity; the patients' own estimate of fitness; joints involved on examination; strength of grip; erythrocyte-sedimentation rate; hæmoglobin and white-cell counts; sheep-cell agglutination titres; toxic reactions and complications; the number and type of analgesic tablets taken daily, and (initially and at 18 months) X-rays of hands and wrists.

The results at 18 months indicated that patients who had the full course of 1 g. of gold salt showed distinct improvement over the control group from the 3rd month onwards, and this favourable difference continued until the 18th month. No significant difference between the groups was noted in the radiological progression of the disease in the hands and wrists. (There will be further assessments at the 30th month.)

Chloroquin

A. J. POPERT, K. A. E. MEIJERS, J. SHARP, and Miss F. BIER (Manchester) reported the results of a trial of chloroquin phosphate in a hundred and twenty-five patients. Alternate patients were treated with tablets containing either 250 mg. or 2·5 mg. of chloroquin phosphate and their progress was assessed clinically and radiologically at 6 months and after 1 year. Chloroquin was given in addition to any other treatment the patients would normally have received, except that gold salts were not given concurrently. Patients on the higher dosage of chloroquin showed a significant improvement in terms of clinical and laboratory criteria, but both groups showed equal radiological evidence of progression of the disease.

Immobilisation

R. E. H. PARTRIDGE and J. J. R. DUTHIE (Edinburgh) described a trial of the effect of complete immobilisation of the joints. Forty patients were admitted to hospital for 6–8 weeks, and all were given calcium aspirin gr. 60–80 daily. They were randomly allocated to two groups. Twenty patients were immobilised in plaster splints in bed for 4 weeks, and no other form of treatment was used. The other twenty were confined to bed for 4 weeks but treated by maintenance exercises, rest splints, and physiotherapy. Subsequently both groups were treated along similar lines; weightbearing was resumed and more active forms of physiotherapy were employed. Functional capacity, disease activity, and the range of joint movement in the two groups were assessed on admission, and at 4, 6, 12, and 24 weeks after admission. The results indicated some advantage for those patients completely immobilised, but the numbers were too small for statistical analysis. There was no suggestion of ankylosis developing in any of the completely immobilised joints.

Reviews of Books

Deafness

JOHN CHALMERS BALLANTYNE, F.R.C.S., D.L.O., consultant ear, nose and throat surgeon, Royal Free Hospital and Royal Northern Hospital, London. London: J. & A. Churchill. 1960. Pp. 254. 25*s*.

Mr. Ballantyne has achieved his object: a comprehensive and readily comprehensible account of deafness, as it affects people of all ages and in all its aspects—medical, educational, psychological, and sociological. Most of the important diseases associated with deafness are briefly discussed, with comments on treatment. The anatomy and physiology of the hearing mechanism are described clearly and simply. All the various tests of hearing are fully explained. Recent advances in design and the increasing usefulness of hearing-aids are dealt with in adequate detail. Most of the illustrations are good, though some of the earlier diagrams could be improved. This balanced account will complete the picture for many who come into contact with some of the aspects of deafness, and it will help particularly those concerned with the disability of deafness from any cause.

The section on perceptive deafness is particularly good; and the modern methods of diagnosis and management of congenital deafness are extremely well discussed in an easy style. Though some readers with a less complete scientific background may feel that too many authorities are quoted, they cannot deny that the chapters are well documented; a useful bibliography is included and there is a good index. This excellent monograph successfully combines modern British otological and audiological practice, and it will be read with pleasure and profit by otologists, teachers of the deaf, social workers, and many others. The publishers are to be congratulated on a very attractive volume at a reasonable price.

An Introduction to Human Blood Groups

FULTON ROBERTS, M.D., fellow of Jesus College, Cambridge; lecturer in pathology, University of Cambridge. London: Heinemann Medical Books. 1960. Pp. 85. 9*s*. 6*d*.

THIS book begins by explaining how antibodies are produced, and then gives a remarkably clear account of the rhesus blood-groups, their discovery, detection, and importance. The minor blood-groups are dealt with briefly. The ABO group comes later because it displays unusual features, such as the presence of natural antibodies. Very short chapters explain the importance of the blood-groups in disease and in the study of genetics and of anthropology, and finally some points that are the subject of current research are briefly discussed. This is a large programme for a short monograph, but the author does not waste a word and his book can be confidently recommended to those seeking a sound basic knowledge of blood-groups but having neither the time nor the inclination to explore the larger volumes filled with curious symbols.

Hypnotism for Medical and Dental Practitioners

A. A. MASON, M.B., clinical assistant, psychiatric department, West London Hospital, and director of studies, Dental and Medical Society for the Study of Hypnosis. With chapters on hypnosis in dental surgery and obstetrics by K. DAWSON WATTS, F.D.S. R.C.S.E., and S. D. PERCHARD, M.D., M.R.C.O.G. London: Secker & Warburg. 1960. Pp. 223. 30*s*.

THIS book makes available to the general reader the lectures to medical and dental practitioners on the basic theory and practice of hypnosis given for the Dental and Medical Society for the Study of Hypnosis. Dr. Mason, whose work in the rare disease congenital ichthyosis has led to the widespread use of hypnosis in many skin diseases, often with marked success, has great experience of his subject. Happily, he has retained his scientific objectivity and emphasises at every opportunity the need for controlled experiment and for checking of results by other observers. He is concerned in this book with the treatment of patients, so there is a minimum of historical and theoretical matter. Techniques of hypnotic induction, the levels of the hypnotic trance, and its nature, are considered in the opening chapters. Then come chapters on the indications for hypnosis (the removal of pain, in psychosomatic medicine, and for modification of the mental state) and hypnotic phenomena: rapport, trance states, sensory and special-senses phenomena, and effects on motor function. A chapter on hypnosis and the problem of perception traces the connection between the theories of Locke, Freud, and modern psychologists, and discusses the phenomena of age regression, of learning, and of time perception under hypnosis.

The chapters on hypnosis in dental surgery and obstetrics provide a sound practical introduction to its use in these fields. There are short bibliographies at the end of each section, and some good illustrations of medical and dental cases.

As the late Prof. Alexander Kennedy says in a preface, it is to be hoped that some knowledge and experience of hypnosis will eventually be part of the medical curriculum.

The Essentials of Perimetry

HOWARD REED, M.S., F.R.C.S., department of ophthalmology, University of Manitoba. London: Oxford University Press. 1960. Pp. 192. 45*s*.

LUCIDLY written and illustrated, this book is remarkable for its simplicity of exposition of the principles and routines for the detection of visual field defects. The emphasis on diagnosis through rapid yet accurate methods of examination will appeal particularly to physicians and neurologists. The text is admirably illustrated by simple line drawings of anatomical features and the essential shape of field defects for 1 or 2 isopters. The book is divided into three parts: applied anatomy of the visual pathway; the visual field and its assessment; and field defects and their interpretation. A select bibliography points to further reading.

Surgical Treatment of Facial Injuries (2nd ed. Baltimore: Williams & Wilkins. London: Baillière, Tindall, & Cox. 1959. Pp. 1117. 256*s*.).—This is a big book, too heavy for armchair reading, and at first sight rather costly. Since the first edition in 1949, six new chapters and 400 illustrations have been added, and the book is double the size. Nearly a third of it is devoted to jaw injuries, with the dental as well as the surgical aspect handled in considerable detail. Then follows a considerable section describing all plastic surgical methods. Deformities are dealt with regionally, with excellent chapters on the eyelids and the nose. In fact, each section is almost a textbook in itself, and the authors, Dr. V. H. Kazanjian and Dr. J. M. Converse, both well-known American plastic surgeons, have set out to cover the subject very thoroughly. The illustrations (line drawings and photographs) are excellent throughout, and greatly enhance the book's value.

Travaux Scientifiques (Bucharest: Edition de l'Académie de la République Roumaine. Paris: Masson. 1959. Pp. 616).—The late Prof. J. Nicolesco wrote some 200 scientific papers and 18 on contemporary medical life and medical history. This well-illustrated memorial volume contains many of his scientific papers arranged in the form of a textbook of neuropathology. The foreword is by Dr. Van Bogaert and the preface by Prof. St. G. Nicolau. It was a happy thought to produce this volume, a well-deserved tribute to the memory of a great scientist.

Triennial Statistical Report, 1955-1957, The Bethlem Royal Hospital and the Maudsley Hospital (Shrewsbury: Wilding & Son. 1959. Pp. 94. 10*s*. 6*d*.).—The report, edited by Dr. E. H. Hare, has been compiled with the comprehensiveness, lucidity, and attention to detail which are usual in publications from this source. Comparison with two previous triennia is now possible; but, as the hospitals are served by changeable doctors practising over a vast area, the report remains of limited general value other than as an exhaustive record of the clinical work done in this unique postgraduate centre of psychiatric teaching and research.

Fundamentals of Modern Allergy.—We apologise to Dr. Samuel J. Prigal, the author of this book, for getting his name wrong in our notice of July 2.

THE LANCET

LONDON 16 JULY 1960

An Expanding Syndrome

THREE years ago we commented on a new syndrome of unusual interest—fulminating, atypically situated, and often intractable gastrointestinal ulceration associated with non-insulin-secreting adenomas of the pancreas.[1] This condition has since acquired considerable fame; and it is now eponymously linked with the two American workers who not only recognised the association of the two lesions but also drew attention to gastric hypersecretion as the ætiological connection between them.[2] Careful scrutiny of further cases has led to the recognition that the syndrome may include additional features—namely, diarrhœa, steatorrhœa, and hypokalæmia as related manifestations. These may precede ulcer symptoms by months or years and may in themselves determine a fatal outcome.

Five years before ZOLLINGER and ELLISON published their paper BROWN et al.[3] described a case of islet-cell tumour without hyperinsulinism and without ulceration but with rapidly increasing diarrhœa. The symptoms were completely and, it seems, permanently relieved by removal of the adenoma. Diarrhœa was also mentioned by FORTY and BARRETT [4] and by MOLDAWER et al.[5]; and it preceded manifestations of ulcer in one of the two original cases of ZOLLINGER and ELLISON. In 1957 PRIEST and ALEXANDER [6] reported a case of the "Zollinger-Ellison triad" (pancreatic adenoma, gastric hypersecretion, and peptic ulceration) in which massive electrolyte loss in the fæces was apparently the immediate cause of death; and VERNER and MORRISON [7] reviewed four cases in which diarrhœa and hypokalæmia were prominent and ulcer manifestations never recorded. Of their two personal cases the first was a 67-year-old Negro who had had diarrhœa for ten months and who had lost 34 lb. in weight before he succumbed to his illness shortly after a hernia operation. Just before he died his serum-potassium was 2·4 mEq. per litre: and necropsy revealed a well-encapsulated adenoma in the body of the pancreas. Their second patient, a young man of 19, had been admitted to hospital fourteen times in three years. His dehydration and hypokalæmia at first responded to intravenous replacement therapy; but eventually he lapsed into an irreversible shock-like state with hypotension, dehydration, and a serum-potassium level of 1·7 mEq. per litre. Postmortem examination showed a small pancreatic islet-cell tumour which contained no β-cells. Neither of these patients had had ulcer symptoms, and no evidence of ulceration was found at necropsy. Last year SUMMERSKILL [8] drew attention to masked steatorrhœa as a possible complication; and from Halifax, Canada, has come an excellent retrospective study of a case in which hypokalæmia was the dominant and ultimately fatal feature.[9] Both those papers raised the question how the diarrhœa fitted into the original syndrome pattern—a problem which Dr. RAWSON and her colleagues in Birmingham discuss in an article which appears this week on p. 131.

Two findings have especially impressed the Birmingham workers—the difficulty of obtaining an alkaline sample on duodenal intubation, and the relief afforded by removing the pancreatic adenoma without recourse to gastric resection. The first of these features supports SUMMERSKILL's view that normal duodenal and small-intestinal secretions may be unable to neutralise the enormous quantities of acid gastric juice that pass through the pylorus. In an acid milieu lipase and other small-intestinal enzymes might be not only inactivated but even destroyed—a reasonable explanation for both the diarrhœa and the steatorrhœa. The second finding of the Birmingham group confirms the dependence of the gut manifestations on the pancreatic adenoma. Previous cases had come to operation only when ulcer symptoms had necessitated resection not only of the pancreatic tumour but also of part or the whole of the stomach; and thus no valid comparisons could be drawn between the preoperative and postoperative levels of gastric secretion. The distinct decrease of this level in the Birmingham case after simple resection of the adenoma leaves no doubt about the tumour's direct hormonal influence.

The remaining puzzles include the identity of the pancreatic hormone (the work of GREGORY et al.[10] suggests that it resembles gastrin) and the absence or comparative mildness of ulceration in several reported cases. A massive assault on the gastrointestinal mucosa by gastric acid, sustained enough to interfere with enzyme action in the middle and lower reaches of the small gut, could be expected to produce just the kind of fulminating ulcers that ZOLLINGER and ELLISON originally described. Without wanting to complicate an already complex problem, we should perhaps envisage the possibility that we are dealing here not with one but with several endocrine syndromes. Progress in the past has often been delayed by the mental shelving of endocrine glands as soon as one of their chief hormones was identified. We waited several decades after the discovery of insulin before beginning to take notice of glucagon and other hyperglycæmic substances secreted by the pancreatic islets; and in considering the pituitary, adrenal, parathyroid, and perhaps other glands we still tend to equate anatomical with functional proximity. The pancreatic component of the Zollinger-Ellison syndrome is marked by the diversity of the pathological and clinical pictures. Pathologically all grades of malignancy have been found in the form both of solitary adenomas and of generalised islet-cell hyperplasia: clinically the picture varies from one with no symptoms

1. See *Lancet*, 1957, ii, 1151.
2. Zollinger, R. M., Ellison, E. H. *Ann. Surg.* 1955, **142**, 709.
3. Brown, C. H., Neville, W. E., Hazard, J. B. *Surgery*, 1950, **27**, 616.
4. Forty, F., Barrett, G. M. *Brit. J. Surg.* 1952, **40**, 60.
5. Moldawer, M. P., Nardi, G. L., Raker, J. W. *Amer. J. med. Sci.* 1954, **228**, 190.
6. Priest, W. M., Alexander, M. K. *Lancet*, 1957, ii, 1145.
7. Verner, J. V., Morrison, A. B. *Amer. J. Med.* 1958, **25**, 374.
8. Summerskill, W. H. J. *Lancet*, 1959, i, 120.
9. Charles, B., Cochrane, W. A. *Canad. med. Ass. J.* 1960, **82**, 579.
10. Gregory, R.A., Tracy, H.J., French, J.M., Sircus, W. *Lancet*, 1960, i, 1045.

to that of a rapidly downhill course.[11] Detailed histochemical studies, such as that undertaken by the Birmingham workers, may help to account for these somewhat bewildering differences.

Meanwhile the clinician must look out for a pancreatic lesion not only in cases of atypical gastrointestinal ulceration (especially associated with high gastric secretion) but also when dealing with obscure diarrhœas. We should certainly include the syndrome in the differential diagnosis of ulcerative colitis, regional enteritis, the malabsorption states, Whipple's disease, carcinoid tumours, sprue, and idiopathic steatorrhœa; and CHARLES and COCHRANE [9] have drawn attention to chronic potassium deficiency as a possible presenting picture. The clinical manifestations of this include muscular weakness, polyuria, polydipsia, tetany, vomiting, and cardiac irregularities; and its recognition can be made difficult by the patient's bizarre and even psychotic behaviour.[12–14] The low serum-potassium is usually accompanied by a metabolic alkalosis which reflects the transfer of hydrogen ions from the extracellular fluid into the cells: it can be corrected only by potassium replacement which results in a reverse shift of hydrogen and sodium.[15] The polyuria and polydipsia do not respond to vasopressin; but, despite the tubular damage which tends to result from chronic hypokalæmia, these symptoms too subside on potassium therapy.[12]

Without further clinical data few would wish to generalise on the correct management of the syndrome. ZOLLINGER and his group were driven by bitter experience to advocate not only careful removal of all pancreatic tumours but also total gastrectomy.[11] The Birmingham workers, on the other hand, believe that with only mild ulcer symptoms such an extreme course is unjustified; simple removal of the pancreatic adenoma has so far sufficed to relieve their patient of his symptoms and to reduce his volume of gastric secretion.

Idiopathic Hypercalcæmia of Infants

IDIOPATHIC hypercalcæmia of infants was first described by LIGHTWOOD as recently as 1952 [16]; and yet in the few years since then its peak incidence has passed, and it is now quite rare. This title may cover more than one pathogenic process, for LIGHTWOOD described a relatively benign condition characterised by failure to thrive, anorexia, vomiting, constipation, loss of weight, and often transient uræmia and urinary infections, whereas FANCONI et al.[17] described a malignant form with the additional features of osteosclerosis, hypertension, loud cardiac systolic murmurs, a characteristic facies, and a high incidence of congenital malformations. But intermediate types of cases have now been recognised,[18 19] which suggests that the benign and malignant forms may represent merely opposite ends of a single spectrum. The benign type has been much the commonest, and most of the work on the ætiology of the syndrome has been done on this variety.

One of the most striking findings has been a high rate of calcium absorption in affected infants studied by metabolic balance techniques.[20 21] This suggested overdosage with vitamin D as a possible cause. It could account for the tendency to a low serum-alkaline-phosphatase level and high serum-cholesterol level,[22 23] possibly the osteosclerosis of the malignant syndrome,[22] and possibly too the low serum and urine citrate levels.[24] Moreover the ecology of the syndrome seems at least superficially to be in keeping with this hypothesis; for it has been commonest in the United Kingdom where supplementation of infants' diets with vitamin D has been more generous and widespread than elsewhere,[25] and since such supplementation was reduced about 1957 the incidence has declined. As with overt vitamin-D intoxication the hypercalcæmia responds to treatment with cortisone.[21]

If vitamin D is implicated in idiopathic hypercalcæmia of infants then some affected babies must be over-responsive to its hypercalcæmic action, since (as FORFAR et al.[26] have shown) the vitamin-D intake of many of the affected babies is quite low, and many unaffected babies tolerate considerably higher doses. Not all agree that vitamin D is implicated in this syndrome—partly because of this necessary additional factor of over-responsiveness in many instances, and partly because provocative doses of vitamin D (up to 100,000 units of calciferol a day) have sometimes failed to increase the symptoms, accentuate the hypercalcæmia or increase the retention of calcium more than would be expected in a healthy infant. CREERY and NEILL [20] administered a provocative daily dose of 2000 units of vitamin D and a high calcium intake for thirty-four days to one of their patients with infantile hypercalcæmia who was in the phase of spontaneous recovery. There were no significant deviations in the levels of serum-calcium or blood-urea, and the child continued to improve clinically. BERENDES [27] obtained similar results. BONHAM CARTER et al.,[21] on the other hand, noted apparent exacerbation of the disease in a 9-month-old boy when he was given 10,000 units of vitamin D daily for ten days while in a state of moderate remission. These apparently differing results may be attributable mainly to the infants being in different phases of the disease, for spontaneous recovery with normal tolerance of calcium and vitamin D is acknowledged to be the natural course of benign infantile hypercalcæmia. Opponents of the vitamin-D hypothesis cite also the fact that a remission may not follow withdrawal of vitamin D for many months, suggesting that the

11. Zollinger, R. M., Elliott, D. W. *Gastroenterology*, 1959, **37**, 401.
12. Black, D. A. K., Milne, M. D. *Clin. Sci.* 1952, **11**, 397.
13. Schwartz, W. B., Relman, A. S., Schwartz, W. B. *New Engl. J. Med.* 1956, **225**, 195.
14. Milne, N. D., Muehrcke, R. C., Heard, B. E. *Brit. med. Bull.* 1957, **13**, 15.
15. Cooke, R. E. *J. clin. Invest.* 1952, **31**, 798.
16. Lightwood, R. C. *Proc. R. Soc. Med.* 1952, **45**, 401.
17. Fanconi, G., Girardet, P. *Helv. pædiat. acta*, 1952, **7**, 314.
18. Russell, A., Young, W. F. *Proc. R. Soc. Med.* 1954, **47**, 1036.
19. Rhaney, K., Mitchell, R. G. *Lancet*, 1956, **i**, 1028.
20. Creery, R. D. G., Neill, D. W. *ibid.* 1954, ii, 110.
21. Bonham Carter, R. E., Dent, C. E., Fowler, D. I., Harper, C. M. *Arch. Dis. Childh.* 1955, **30**, 399.
22. Ross, S. G., Williams, W. E. *Amer. J. Dis. Child.* 1939, **58**, 1142.
23. Anning, S. T., Dawson, J., Dolby, D. E., Ingram, J. T. *Quart. J. Med.* 1948. **17**, 203.
24. Winberg, J., Zetterström, L. *Acta pædiat., Uppsala*, 1956, **45**, 96.
25. Morgan, H. G., Mitchell, R. G., Stowers, J. M., Thomson, J. *Lancet*, 1956, i, 925.
26. Forfar, J. O., Balf, C. L., Maxwell, G. M., Tompsett, S. L. *ibid.* p. 981.
27. Berendes, H. *A.M.A. J. Dis. Child.* 1958, **96**, 476.

cause in such cases is not simply an excessive supply of the exogenous vitamin.[28]

Investigations of the hypervitaminosis-D hypothesis by vitamin-D assays on the plasma of affected infants have been difficult to do and to interpret. Thus THOMAS et al.[29] found no increase in vitamin-D activity in the plasma from 2 infants with the benign form of hypercalcæmia, whereas FELLERS and SCHWARTZ,[30] who studied 2 infants with the malignant form of the syndrome, found high plasma levels of vitamin-D activity—greater than in children who had been receiving 100,000 units of vitamin D orally per day—even after seventeen months on a low intake of vitamin D. If this result is taken at its face value it suggests that the infants had some powerful endogenous source of vitamin D or similarly active compound. This possibility has been stressed by FORFAR et al.,[28] who have shown that hypercholesterolæmia, affecting the free but not the ester fraction, characterises idiopathic hypercalcæmia of infants. It is theoretically possible that this free cholesterol fraction contains material with vitamin-D activity which the body has synthesised. FORFAR has further suggested that exogenous vitamin D may activate endogenous vitamin-D precursors as well as exerting its own physiological effect, and that this may explain the hypercalcæmia and increased calcium absorption in infants taking only moderate amounts of vitamin D in their diet. He points to the possible relevance of the fact that hypothyroid children with their typical hypercholesterolæmia are peculiarly resistant to rickets and sensitive to vitamin D.[31]

Idiopathic hypercalcæmia of infants may reasonably be regarded as a syndrome which mimics closely the effects of hypervitaminosis D. Contributory factors appear to be the ingestion of cow's milk (in which the concentration of calcium is at least four times higher than that in human milk), the taking of alkalis, infections, and, of course, the administration of large doses of vitamin D, sometimes unwittingly, in fortified infant foods. It is reassuring to learn from a recent follow-up study by MITCHELL[32] of 13 benign cases of infant hypercalcæmia that there was no evidence of a persisting impairment of renal function.

28. Forfar, J. O., Tompsett, S. L., Forshall, W. *Arch. Dis. Childh.* 1959, **34**, 525.
29. Thomas, W. C., Jr., Morgan, H. G., Connor, T. B., Haddock, L., Bills, C. E., Howard, J. E. *J. clin. Invest.* 1959, **38**, 1078.
30. Fellers, F. X., Schwartz, R. *A.M.A. J. Dis. Child.* 1958, **96**, 476.
31. Fanconi, G. *In* Ciba Foundation Symposium on Bone Structure and Metabolism (edited by G. E. Wolstenholme and C. M. O'Connor); p. 189. London, 1956.
32. Mitchell, R. G. *Arch. Dis. Childh.* (in the press).

Annotations

THE NEW AFRICAN MEDICAL SCHOOL

INSTEAD of building the hospital for Europeans for which £1 million has been set aside in their development plan, the Federal Government of the Rhodesias and Nyasaland have decided to build a teaching hospital, both for Europeans and non-Europeans, in conformity with the recommendations of the Rhodesia Medical School Planning Committee.[1] This decision, announced by Mr. Goldberg, the Minister of Health, on July 6, is in present circumstances an act of courage. Where excuses could so easily be found for taking a short view, the Government have taken the long one.

The reasons why the Federation must have its own medical school, where European, African, and Asian students can all receive first-rate training against an African background, were clearly set out by the planning committee; and the arrangements by which Birmingham University will sponsor the new school have conspicuous advantages for both sides.[2] For building this school, beside the proposed teaching hospital, the University College of Rhodesia and Nyasaland has to find some £750,000 beyond the £250,000 promised by the Nuffield Foundation; but for so important a purpose this should and must be feasible. The scheme is important in at least three ways—first, because it is the only practicable means of providing doctors for these territories; secondly, because fulfilment of the committee's plans[3] would make it one of the world's most interesting projects in medical education; and, thirdly, because it is a resolute attempt to pursue civilisation instead of prejudice. Though civilised solutions are the only ones with any lasting value, the odds against them always seem great; and the Federal Government has earned respect by choosing what is ultimately right rather than what might be more convenient.

1. First report of the Medical School Planning Committee (chairman: Mr. L. Farrer-Brown). *Centr. Afr. J. Med.* 1958, **4**, 269 (suppl.).
2. See *Lancet*, 1960, i, 331.
3. Second report of committee. *Centr. Afr. J. Med.* 1959, **5**, 145 (suppl.). See *Lancet*, 1959, i, 929.

PERTUSSIS TODAY

THE incidence of pertussis has declined notably in the past ten years: notified cases have decreased from 146,000 to 33,000 per year. Clinically the disease seems less severe, and the mortality has fallen from about 600 to 20 deaths per year. But pertussis remains an enigmatic disease, difficult to diagnose, stubbornly resistant to treatment, and trying for both the child and parents. Inevitably the clinical diagnosis is made late, because the paroxysmal cough takes so long to appear. In an outbreak early diagnosis would do a lot to limit the spread of the disease; and Donaldson and Whitaker[1] have now described a technique of fluorescent-antibody staining of nasopharyngeal smears which they claim is reliable and rapid, providing a result in an hour. Of 36 cases where the patients had symptoms and signs of pertussis, the test proved positive in 31; 13 patients who had been treated with antibiotics for less than forty-eight hours all had positive tests; but of 18 patients treated with antibiotics for more than forty-eight hours only 2 had positive tests. This method, if its value is confirmed by other laboratories, will surely find a place in the prompt diagnosis of pertussis.

After diagnosis, what is the treatment of choice? We have moved but little forward from the end of the 18th century when William Moss wrote[2]:

"when the complaint takes a favourable turn it is frequently attributed to the means that were last used: hence that means is ever after recorded as infallible. As it is a disease of the spasmodic or convulsive kind it has been sometimes relieved, or even removed by a shock or sudden fright: thus riding upon a bear (a frightful mode of travelling no doubt) from the fright it occasions has been said to be serviceable".

1. Donaldson, P., Whitaker, J. A. *A.M.A. J. Dis. Child.* 1960, **99**, 423.
2. Cited by G. F. Still. The History of Pædiatrics; p. 474. London, 1931.

Claims are still made for every new treatment. In a recent review of a ten-year study of pertussis, hyperimmune gamma-globulin was strongly recommended, although "biostatical proof is lacking as to its efficiency".[3] A carefully controlled trial showed that there was no evidence that this had any effect on the disease.[4]

Since pertussis is still lethal to children, particularly under 1 year old, every effort should be made to immunise those at risk. This, with early diagnosis and isolation, and with antibiotics to control secondary infection, should further reduce both the incidence and the severity of pertussis.

GROWING UP TODAY

As Dr. Alex Comfort has lately reminded us in a broadcast,[5] young people are growing up faster nowadays. During the past century the age of puberty has come down from about seventeen to thirteen years, and not only has growth been speeded but the final sizes attained are larger. Vigorous, thriving teenagers are a welcome addition to the nation, but there have been signs that early development is causing difficulties for some. For instance, a disturbing increase in cases of gonorrhœa in the 18–19 age-group [6] was reported some months ago, and last week the National Council for the Unmarried Mother and Her Child recorded [7] their grave concern at the extreme youth of so many of the girls who came to them for help. The Council see with regret many girls whose youth renders them incapable of supporting or understanding the responsibility of motherhood, with their school lives broken and disrupted, and their home conditions unnaturally complicated.

Many young people seek to solve their problems by early marriage and in this they are helped by high wages and hindered by the housing shortage. But it is a solution which may impose responsibility prematurely, and the Council are receiving an increasing number of letters from married couples who ask "if we can treat their legitimate children as illegitimate and help to get them adopted". Some of these are young couples who are students; others are living in expensive furnished rooms with heavy hire-purchase commitments; others have been forced into marriage by their parents.

Sex education seems a sensible way of meeting the situation, but the needs of some children at any rate will not be met by conventional notions of content and timing. At least one London school teacher [8] in conversation with a class of 14-year-old boys living in a so-called tough area was met with requests not to "give them any of this birds and bees nonsense". Many of the boys had already had sexual experience and their concern was for information on such topics as "how can I avoid getting V.D.?" These young people are of course only a minority of their age-group. But the whole cohort is living in a world to whose difficulties their elders have made a substantial contribution. The social pattern is changing only slowly in response to modifications in the physiological pattern; and meantime many of our customs and values are actively unhelpful to those who have had physical maturity thrust upon them at a time which is inconvenient to society but may be biologically appropriate.

3. Kaufman, S., Bruyn, H. B. *A.M.A. J. Dis. Child.* 1960, **99**, 417.
4. Morris, D., McDonald, J. C. *Arch. Dis. Childh.* 1957, **32**, 236.
5. *Listener*, July 7, 1960, p. 25.
6. See *Lancet*, 1960, ii, 1396.
7. Report for 1959–60. Obtainable from 21, Coram Street, London, W.C.1.
8. *Guardian*, July 4, 1960, p. 8.

TREATMENT OF ADVANCED BREAST CANCER

DESPITE many reports in the past decade on the use of androgens and œstrogens in metastatic breast cancer, doubt still surrounds some aspects of this treatment. In the last of a series of reports which began in 1947 the American Medical Association [1] describes a twelve-year collaborative study of the effects of administering androgens or œstrogens to nearly two thousand patients with disseminated breast cancer.

Of the 1983 cases submitted, only 944 were included in the analysis. Of these, 580 were treated with various androgenic hormones, and in this group the overall regression-rate was 21·4% (regression was strictly defined as a distinct and measurable decrease in one or more of the dominant metastatic lesions with no progression of any other metastases and no evidence of new growth). Androgen treatment was as effective in premenopausal as in postmenopausal women and was equally effective against metastases in viscera, soft tissue, and bone. Patients who responded to treatment survived significantly longer than those who did not respond (nineteen months compared with ten months). The regression-rate in 364 patients treated with various œstrogens was 36·8%; this group included only 7 premenopausal patients. The average survival of patients who responded to treatment was 27·3 months, compared with 10·4 months in those who failed to respond—a highly significant difference.

Direct comparison of the regression-rates with androgens and with œstrogens would not be valid since a substantial proportion of the patients treated with androgens were premenopausal. When the whole series was broken down according to age, there appeared to be a higher remission-rate with œstrogens than with androgens; but the differences were not significant except for the group aged 70 and above. With œstrogens, the remission-rate for soft-tissue lesions (breast, skin nodules, and lymph-nodes) in postmenopausal women was 40·7%, whereas with androgens it was only 18%. Moreover œstrogens were at least as effective as androgens in the control of skeletal metastases. The older the patient at the start of treatment with either type of hormone, the greater was the chance of regression. In cases where the menopause intervened between the primary treatment and recurrence the free period was over seven years (compared with roughly three years in others).

When administration of hormones to patients with disseminated breast cancer fails to check the disease, the last effective treatment is endocrine ablation. Three papers concerned with this subject have lately appeared in these columns. Mr. Atkins and his colleagues [2] at Guy's Hospital compared the clinical results of adrenalectomy with those of hypophysectomy, the patients being randomly selected for either operation. Hypophysectomy proved marginally the better operation, judged by the state of the patients three months after operation and the length of survival. These workers found no relation between the response to hormone administration and to ablative treatment. The longer the duration of the disease, the greater was the chance of remission. The Guy's workers [3] reported two years ago that the ratio of the 11-deoxy- to the 11-oxy-17-ketosteroids (determined before operation) correlated with the patient's response

1. *J. Amer. med. Ass.* 1960, **172**, 1271.
2. Atkins, H. J. B., Falconer, M. A., Hayward, J. L., MacLean, K. S., Schurr, P. H., Armitage, P. *Lancet*, 1960, i, 1148.
3. Allen, B. J., Hayward, J. L., Merivale, W. H. H. *ibid.* 1957, i, 496.

to treatment. Dr. Bulbrook and his colleagues [4] have claimed that urinary assays of 17-hydroxy-corticosteroids and ætiocholanolone may be of value in selecting patients likely to benefit from hypophysectomy and rejecting those who will not benefit. We hope that this claim will be tested in a clinical trial; for, if it proves to be well founded, a substantial number of women with breast cancer can be spared unnecessary major surgery. By contrast Mr. Forrest and his colleagues,[5] in a thorough investigation of urinary œstrogen levels of patients before and after pituitary destruction, oophorectomy, and adrenalectomy, found no correlation between œstrogen excretion and the response to treatment. They conclude that "there appears to be little justification for continuing the practice of referring to breast tumours which respond to endocrine ablation as œstrogen-dependent".

It may seem anomalous that androgen and corticoid metabolites may be useful for prognosis while the œstrogens are not, since theoretically the converse might have been expected. These results, and those described in the American Medical Association's report, indicate how little is yet known about hormone-dependence in breast cancer despite several decades of investigation.

HOSPITAL DESIGN

SUDDENLY the architectural world has found itself with plenty of reasons for taking note of problems in hospital planning and design. On July 7 a Ministry of Health exhibition of hospital design and building was opened at the Royal Institute of British Architects; the same day the *Architects' Journal* published a special issue on hospitals; this week some 400 architects have been attending a hospitals course at the R.I.B.A.; and in September the Nuffield Foundation is holding in Oxford a residential course for young hospital architects. All this is to the good even if the visitor to the Ministry's exhibition is left with the depressing feeling that it should all have been done long ago.

The exhibition is divided, broadly, into six sections—general hospitals, teaching hospitals, psychiatric hospitals, special departments, "interesting schemes", and trends in ward design. These six sections are accompanied by some twenty different models. The aims of the exhibition are (1) to show what progress is being made and what the new hospitals are like and (2) to impress on architects the growing scope for creative skill in this field. Bringing together, at it does, the plans and the models of so many of the new hospitals, the exhibition can rightly claim to depict progress. But is this progress always enlightened? Why, for example, are some of the wards at the new Cardiff Hospital sited at the bottom of an 8-storey well? Why, at the same hospital, are nurses on night duty to be housed in a separate block of flats? Cannot the rooms in the nurses' home be rendered sufficiently sound-proof to prevent the nurses on night duty being disturbed? Is the seventh floor of the Welwyn and Hatfield Hospital the best place for the X-ray department? In the section dealing with special departments, why are the only exhibits a metabolic unit, an outpatient department, and a boiler-house? Where are the pathological laboratories, the X-ray departments, the kitchens, and the laundries? Why is the 36-bed ward of the Bellshill Maternity Hospital served by only two bathrooms? Such questions arise throughout the exhibition. But, among some uninspired models and uninteresting stands, there is a bright spark: the model of the hospital at Wrexham Park, Slough. This, with its central administrative tower and everything else at ground level, is a stimulating and imaginative exhibit—although clearly only the smaller hospitals could be designed in this way.

In the special edition of the *Architects' Journal* the editors, under the title of "The Hospital Brief", have gathered papers on subjects as far apart as "The Teaching of Medicine" and "The Laundry". Most of the sixteen articles deal with function in some form or another. All are forward-looking and should be of the greatest assistance to hospital architects. Fully half the articles some from north of the Border where, in the words of the introduction, "there is some practical experience of ideas which in England are still only being discussed".

Fortunately, the two courses for hospital architects seem to be concerned with the function of hospitals in the future; and we hope that in them emphasis is given to the needs of the special diagnostic departments, for here much leeway has to be made up.

SCIATIC PALSY

OPINIONS on the possibility of recovery after serious injury to the sciatic nerve have been rather curiously divided. Some have been impressed by the possibilities of regeneration along the sciatic nerve and reinnervation of muscle with some return of function, whereas others have been disturbed by the incompleteness of the neurological recovery and the incidence of complications such as joint stiffness and trophic lesions. Indeed, they have become so despondent that they would be reluctant to advise repair of a seriously injured sciatic nerve and would recommend amputation instead.

Such extreme optimism or pessimism can be rationally countered only by a long-term follow-up of a large number of cases. Reports by Clawson and Seddon [1 2] go a long way towards providing data on which a reasoned judgment can be made. They have reviewed 145 patients who were observed from three to eighteen years after repair of the sciatic nerve or its branches. Most of the repairs were done during or immediately after the 1939–45 war; and the possibility of a long-term follow up of this sort owes much to the prescience of the late George Riddoch, who played a large part in establishing in this country centres for the treatment of peripheral-nerve injuries.

It is essential to define what we mean by recovery after nerve injury, and to distinguish neurological recovery from usefulness of the limb. After suture of the medial popliteal division of the sciatic nerve, four out of five patients had strong action in the calf muscle, which is the most important and usually the only muscle to recover. In the intervening years some patients have clearly developed strong action in the calf muscle which they did not have when the results were analysed for the Medical Research Council report on peripheral-nerve injuries [3]; at that time just over half the cases had reached this grade of recovery. Moreover, 60% of the patients now have

4. Bulbrook, R. D., Greenwood, F. C., Hayward, J. L. *ibid.* 1960, i, 1154.
5. McAllister, R. A., Sim, A. W., Hobkirk, R., Stewart, H., Blair, D. W., Forrest, A. P. M. *ibid.* p. 1102.

1. Clawson, D. K., Seddon, H. J. *J. Bone Jt Surg.* 1960, **42B**, 205.
2. Clawson, D. K., Seddon, H. J. *ibid.* p. 213.
3. Peripheral Nerve Injuries (edited by H. J. Seddon). *Spec. Rep. Ser. med. Res. Coun., Lond.* 1954, no. 282. H.M. Stationery Office, 1954.

some response to touch stimuli on the sole of the foot, compared with 27% at the time of the M.R.C. report.

No such long-term improvement has occurred in recovery of the lateral popliteal nerve after suture, and at this later review only about a third of the patients could dorsiflex the foot against gravity and resistance. Clawson and Seddon show that with injuries to the lateral popliteal nerve the general standard of recovery was poor and was no better in cases where suture was undertaken early; whereas with injuries to the medial popliteal nerve, results are better where suture was prompt.

The problem of gaps in the sciatic nerve following gunshot wounds has usually been overcome by mobilisation of the nerve and flexion of the knee, followed by gradual stretching for several weeks. There was at one time considerable scepticism about the value of a nerve suture which had to be followed by considerable stretching of the nerve, but this long-term follow-up shows that gaps of 12 cm. can be closed with as much motor recovery as after repair of smaller gaps. Indeed, the only alternative to direct suture is to insert a nerve graft; and, no matter what the technique of grafting, the results are poor.

Clawson and Seddon [2] mention several examples of patients with complete sciatic palsy who are engaged in strenuous occupations with virtually no disability. These workers have undertaken the difficult but valuable task of correlating the usefulness of the limb with the grade of neurological recovery. Almost all the patients with palsy of the lateral popliteal nerve who had good motor recovery also had good function; but a surprisingly large proportion (83%) of those with poor motor recovery had satisfactory function. More than four-fifths of the patients with medial popliteal nerve palsy have a satisfactory functional result, whether the neurological recovery is good or bad, but on the whole those who have a better neurological recovery have a better grade of functional recovery in the limb.

It is quite clear, therefore, that factors other than nerve regeneration play the most important part in giving the patient a useful limb. More than half the patients with lesions of the medial popliteal nerve are over-responsive to pinprick; this is a disabling state at first, but one which gradually becomes less important, and can be made less troublesome by wearing a thick rubber pad inside the shoe. 8 out of 12 patients who had a lesion of the posterior tibial nerve at the ankle exhibited over-response; and it is questionable whether suture of the posterior tibial nerve should be done at all, because over-response may be more of a disability than loss of sensibility.

Perhaps the most serious complicating factor is deformity of the limb; for it is fixed deformity rather than loss of sensibility that is most likely to give rise to pressure sores—one of the most disabling complications that can arise from sciatic palsy. Amputation was sometimes required on account of pressure sores with fixed deformity, and in these cases the operation was worth while. Where amputation was done for pain there was little or no improvement, and it is noteworthy that amputation was done in only 10 patients out of a total of 329 with sciatic nerve lesions.

This long-term follow-up provides evidence that one of the most important aspects of treatment is the maintenance of mobility in the limb and the prevention of deformity. With a mobile foot in a good position the patient will probably have satisfactory function no matter what the grade of neurological recovery.

THE INEFFECTIVE TOOTHBRUSH

THE design of the toothbrush has changed little in the past hundred and thirty years. A plate in Maury's treatise on dentistry,[1] published in 1833, shows that almost every shape of brush had already been thought of—including one pattern that was reinvented in time for a recent dental congress.

The figures for the number of toothbrushes sold in Great Britain are depressing—less than 25 million toothbrushes for 35 million potential users in 1956. Most people think of the toothbrush as a semipermanent article that remains useful until it is reduced to a splayed-out collection of disheartened bristles. The public are loath to pay more than about two shillings for a brush, thus restricting enterprise by the manufacturers. Advertising has little effect on sales; but branded makes by well-known firms sell more readily than those comparatively unknown, even if of equal merit.

A few years ago, there was a move to rechristen the toothbrush a "mouthbrush" as a title more truly indicating its function. Proper brushing helps to keep the epithelium of the gingivæ well keratinised, and will remove the bacterial plaque on the surface of the tooth [2] (the "yellow film" beloved of the advertisers). This is, of course, an æsthetic and hygienic improvement; but if there is to be any real hope of preventing caries, thorough brushing must be carried out at least four times a day—for which few have either the time or the inclination. The various toothbrush-drills taught by dental surgeons are difficult to carry out correctly. The awkward up-and-down movements easily degenerate into narrow, elliptical loops, not far removed from the to-and-fro scrubbing action which leaves even the most accessible interdental spaces packed with food debris. Too much reliance is probably placed on medicated toothpastes: no dentifrice can ever be more than a detergent, in the true sense. The inclusion of hexachlorophene, sodium ricinoleate, or sodium fluoride is of negligible value.

Obviously some new approach to tooth-cleaning is needed, and this has been made by Archer et al.[3] who have produced some interesting variants on the conventional brush. One design is for a portable brush in a cylindrical case which carries a supply of toothpaste; another is for a disposable brush, the semiflexible handle of which contains paste that can be forced through a small nozzle among the bristles. An even more unorthodox design has no bristles, the cleansing being done by a series of small-diameter nozzles supplied with water from the bathroom tap. Archer et al. suggest that a small block of detergent could be incorporated in the handle to make the instrument more pleasant and effective. Rubber or bristle gum stimulators could be fitted easily, and a mouth-spray based on these designs (which the authors admit are purely tentative) might prove acceptable and effective.

Lord ADRIAN has been elected president of the Royal Society of Medicine in succession to Sir GEOFFREY MARSHALL.

1. Maury, F. Complete Treatise on the Dental Art. Paris, 1853. Plate reproduced by R. Lucock Wilson. The Story of Dentistry; p. 20. London, 1958.
2. Arnim, S. S., Williams, Q. E. *Dent. Radiog.* 1959, **32**, 61.
3. Archer, B. L., Bernaston, J., Grieves, J. *Design*, July, 1960, p. 24.

Special Articles

RAMPTON—A SPECIAL HOSPITAL

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THE Press and the public are keenly interested in the three State institutions—Moss Side, Broadmoor, and Rampton—but discussion of the social and medical issues raised by their management is often hampered by lack of information. We hope, therefore, that our description of Rampton, the largest of these hospitals, and its work will be useful.

BACKGROUND

Rampton was built by the Home Office and opened in 1913 as a criminal lunatic asylum (250 beds). The asylum was closed in 1920, and the buildings were taken over by the Board of Control under the Mental Deficiency Act 1913 and named Rampton State Institution. The National Health Service Act 1946 provided that this should be managed by the Board of Control on behalf of the Minister of Health. Under the Mental Health Act 1959 the Ministry will administer the State Institutions (in future to be called Special Hospitals), and on the dissolution of the Board of Control will become responsible for their direct management.

Buildings.—The hospital and grounds cover 200 acres about seven miles from Retford, Nottinghamshire. A central three-storey block is divided into wards, with many single bedrooms, which house nearly half the patients. In the block the standard of security is high. Almost all patients spend the first part of their stay there. Beyond this main building are 17 self-contained villas. Each ward or villa has 35–40 patients. To the front of the hospital are 140 staff houses, and within the grounds are recreation grounds, a small pig farm, vegetable gardens, maintenance shops, power-house, and sewage farm.

Staff.—There are 7 doctors, 1 psychologist, 1 psychiatric social worker, and a resident chaplain.

153 male nurses are supervised by the chief male nurse, his deputy, and assistants, while 115 women nurses are supervised by the matron, her deputy, and assistants. The chief occupations officer is a man and the head occupational therapist a woman. The preliminary training school for nurses offers a three-year course for the General Nursing Council's mental-deficiency certificate. Except in the early training years, there is little wastage of staff, particularly among the men. Each year a small number are seconded for general-nursing training.

THE PATIENTS

Patients are admitted by the Board of Control only on evidence of " dangerous and violent propensities ". They may be admitted from their own homes or from mental-deficiency hospitals as well as from prisons, borstals, or approved school. A high proportion of male patients have sex disorders. Though the behaviour of many has been violent before admission, few have committed murder; most of those that have are detained under Home Office order as " Her Majesty's pleasure " cases. Among the women a common syndrome is an outburst of hysterical aggression and violence, at times accompanied by self-injury.

The annual admission-rate varies from 50 to 150. There are twice as many men as women, and far fewer women arrive from the penal institutions or courts. The usual age of admission is between sixteen and thirty years. There is no upper or lower age-limit. The very small number of children live in a separate area apart from the main building. They are usually of lower grade than the general run of patients, and respond well to the individual care they receive.

Intelligence

The intelligence range of many patients lies between 75 and 85 I.Q., but in recent years increasing numbers of low-grade patients and of epileptics have been admitted. On admission the intelligence of the women is somewhat lower than that of the men.

Clinical Status

About a tenth of each year's admissions are low-grade patients—i.e., idiots, and imbeciles—and many of these show gross neurological dysfunction. A very small proportion of each year's admissions show psychotic symptoms, but these are rarely specific or pronounced enough for the patient to be classified as a psychotic rather than a mental defective. Frank psychotics are usually removed from Rampton to a mental hospital.

Epileptic patients are likely to become a problem in the future because of the difficulty of returning stabilised epileptics to the community. At present there are at Rampton 97 male epileptics and 86 female epileptics (compared with 72 and 58 in 1952) though many have ceased to have fits after a short period in hospital.

More than half of each year's admissions are feeble-minded young men and women, educationally retarded, emotionally blunted or overreactive, with histories of distressing early upbringing or trauma, and only an elementary appreciation of the need for some personal responsibility and satisfactory interpersonal relationships. Occasionally they have neurotic symptoms and show extreme egocentricity.

Discharges

Before the Board of Control authorises a patient to leave Rampton Hospital, the medical superintendent must report to them that the patient is " no longer of dangerous or violent propensities ". A patient who has been sentenced to detention in a prison, borstal, or approved school may not be transferred before the end of his sentence without Home Office consent. During 1959, excluding transfers to mental hospitals and Moss Side Hospital, 70 men and 57 women left Rampton, a few for their homes or agricultural hostels and the rest for local hospitals. Moss Side has the same function as Rampton, but is smaller.

An analysis of the patients at Rampton in 1959 showed that only 7% of the men and 4% of the women admitted before 1950 were still in the hospital. These patients who remain are an increasing residue of physically deteriorated and older people, amounting to about a quarter of the present hospital population.

PSYCHIATRIC TREATMENT

Psychiatric therapy differs somewhat for men and women patients. Chemotherapy appears to be more essential for women, though during the past eighteen months we have reduced nightly sedatives from about 140 to 20. Formal individual deep psychotherapy is seldom practised,

though eclectic counselling is a daily function of all the medical staff. Formal group therapy is being tried experimentally. Self-organised entertainment is one means of developing normal interpersonal relationships, and concerts, plays, dances, and sport have always been given high priority. Television and films are available for all patients, though no claim is put forward for their therapeutic effect.

Electroshock has been found to have a limited application, but it has been largely superseded by chemotherapy. The hospital has never had need of an insulin unit, but a series of prefrontal leucotomy operations were carried out on severely disturbed women patients during 1952–54.

TRAINING

Educational retardation is an almost inevitable result of the longstanding general social maladjustment of most patients. Regular classes are held by the resident teacher, with help from other members of the staff, for the most severely retarded. Many patients have strong inferiority feelings over their illiteracy and try to conceal it. There is often a resistance to school attendance. Because the abilities and needs of patients vary widely, many classes are needed.

Except for a small group of disturbed or physically deteriorated patients, all spend about six hours daily in the workshops. The range of employment is very wide.

During the early part of his stay a patient is employed in indoor workshops; but, health permitting, he graduates to less restricted work in the gardens and farms. No patients are employed outside the hospital grounds.

To leave Rampton Hospital—to go to a mental-deficiency hospital, hostel, or to go home—is a sudden change; and relapse, if it comes, often comes during the first few weeks after discharge. With the present system there is usually a few months between the date that a patient is approved for transfer and the date he finally leaves. This offers an opportunity for rather intensive resettlement training.

The patients awaiting transfer meet weekly, as a group, for an afternoon session with a doctor, a psychologist, and a social worker. The aim is to start informal discussions on topics likely to be important to the patient when he leaves. A loose programme is followed for about four months, during which time the group changes as members leave and others join. Two persisting aims are to make the patients aware of the hazards to them of social frustration, loneliness, and social inadaptability, and to remove the barriers they perceive between themselves and " authority ". Much of the apparent success of this scheme is due to visiting speakers, who have included representatives of the Ministry of Labour, National Assistance Board, police, probation, employers, local mental-deficiency hospitals, and Toc H. Films dealing with social issues are popular and useful to initiate discussion. The greatest problem has been to get patients to attend voluntarily.

Many patients discharged from Rampton after a stay of some years have had virtually no experience of ordinary social life as adults. Doctors, employers, workmates, landladies, and neighbours are likely to view them with concern, and they often lack the security of a firm family background. Aftercare is at present the responsibility of the hospital or local authority to which a patient is removed, but it is also the active concern of the psychiatric social worker at Rampton, who tries to maintain the patient's contacts with relatives and friends from the day of admission.

RESEARCH

During recent years research has centred on the assessment of stability, prognosis, and relapse; for these are vital to many of the therapeutic and social issues which concern the hospital.

A follow-up of discharged male patients [1] has shown that, though the average length of stay is long (7–11 years), there is a high positive correlation between length of stay and successful discharge. It is the length of stay that appears to be associated with success, rather than the age of transfer. Age on admission is not significant, but classification according to conduct disorder—e.g., sex, homosexuality, violence, larceny, and so on—suggests that these groups carry different relapse potentialities. A history of repeated larceny is most highly linked with relapse. Though about a third of the discharged patients relapse, their behaviour is far less serious than their behaviour before their stay at Rampton. Relapse is more probable when the patient returns directly to his home than when he returns to society gradually through a local hospital. Behaviour within the hospital is a fair indication of later success or relapse; the most important contraindications are frequent aggression, attempts to escape, and, possibly, damage to property.

At present the length of stay necessary for young, grossly unstable, feebleminded patients, is probably greater than for any other comparable group of patients, except schizophrenics. Evidence firmly based on research is probably the best stimulus for major therapeutic developments which will reduce the length of stay in hospital and prevent relapse.

DISCUSSION

Within a framework of security, and within the limits of our present-day rudimentary knowledge of psychopathy and conduct disorders, the Institution functions as a hospital. All but a small proportion of the patients are ultimately discharged and only a few relapse. Furthermore, relapse is not necessarily serious and offences are, in fact, more likely to be acquisitive than aggressive.

To some extent, and for some time to come, treatment must be empirical, and occupational activity must play a large part. At Rampton, as elsewhere, we must consider the possibility of using occupational activities more specifically to fit the discharged patient for assimilation into an urban, industralised community. This in turn presupposes study of the skills of these people and their potential ability.

The Royal Commission recognised that " the patients in Rampton and Moss Side Hospitals probably present more difficult problems than those of any other hospitals in the country ".[2] The typical patient at Rampton is not demented; he may have some literary skill; he is in daily contact with barrackroom lawyers (often very well informed); and he is a patient against his own wishes and often those of his family. Clinical relations, which are always difficult to establish, are often jeopardised by misleading advice from well-meaning friends and relatives.

In the past the hospital has been geared to a programme of training, leading to ultimate discharge. However, there are signs that it may be forced to change its established therapeutic function to a more custodial function if existing trends continue and long-stay cases continue to accumulate.

Though advance in this field will never be dramatic, one can distinguish changes. But, even granted miraculous advances in knowledge, two fundamental difficulties will always remain. Nothing is likely to alter the fact that the

1. Tong, J. E., Mackay, G. W. *Brit. J. Delinq.* 1959, **9**, 276.
2. Report of the Royal Commission on the Law Relating to Mental Illness and Mental Deficiency; p. 27. H.M. Stationery Office. 1957.

majority of patients will be incapable of more than relatively unskilled work and moderate social adjustment, and that they have not, and will not have, the security and support of an interested family and friends. One solution to this latter problem may lie in the organisation of hostels, in both urban and rural areas, staffed by people experienced in work with such patients.

We have drawn freely from the observations of Dr. G. W. Mackay, medical superintendent at Rampton from 1940 to 1958, to whom credit is due for many of the developments described. The paper is published with the encouragement and permission of the Board of Control.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNÆCOLOGISTS

THE new college building, which was to be formally opened by the Queen on Wednesday, occupies a triangular site in Sussex Place on the west side of Regent's Park. Built of brick and Portland stone it comprises an academic wing and an administrative and members block (fig. 1). The front faces the lake in the outer circle of the park, and the back is bounded by Park Road and Kent Passage.

Fig. 1.—Exterior of the College building: academic wing on the left; administrative and members block on the right.

The Academic Wing

The entrance hall, library, and museum are on the ground floor; and the main staircase, lined in elm, leads to the assembly hall and council-room suite.

On the right of the porch is the foundation stone, laid by Queen Elizabeth the Queen Mother in 1957,[1] and on the left is a stone tablet to commemorate the official opening. The entrance hall is lined with Italian marble, and has a plaque bearing relief sculptures in bronze of William Blair-Bell and William Fletcher Shaw—" by whose inspiration, vision and determination this college was founded in 1929 ".

The library, panelled in elm and lined with open shelves, has furniture of beech. In recesses at either end are two bookcases—early Georgian and Chippendale—bequeathed by Professor Blair-Bell, which guard the college's collection of historical books.

The Wellcome research museum, painted pale green, houses pathological specimens in ten specially illuminated bays. A case in the centre holds Chamberlen forceps and other obstetrical relics. A large bay at one end can be used for demonstrations, and the room can be easily rearranged to provide accommodation for examinations.

The Nuffield assembly hall (fig. 2) has African-walnut and marble panelling and a decorative ceiling. Large windows, framed by red velvet curtains, occupy the whole left wall, and reveal a magnificent view over the lake and the park. The carpet, in two tones of grey, incorporates the college coat-of-arms. The 230 walnut chairs have been given by fellows and members of the college, and each bears the carved name of its donor. Sliding panels behind the platform conceal a screen; projection equipment is installed; and the ceiling lighting is suitable for film shows. In addition, an adjacent servery makes it possible for small dinners to be held.

The council-room suite comprises a committee room and the council chamber, which are separated by folding doors, and a robing room. Again carpeted in two-tone grey, the walls and curtains are in soft shades of blue and green. Behind the president's chair, and incorporating the coat-of-arms, is a stained-glass window—the gift of Dame Hilda Lloyd, the only woman who has been president of the college.

At the rear of the first floor are the museum workrooms and the Wellcome research laboratory.

The Administrative and Members Block

This four-storey block includes:

On the ground floor—administrative offices, cloakrooms, and a kitchen.

On the first floor—the president's office, which overlooks the park and is furnished from the bequest of Professor Blair-Bell; and the secretaries' offices, and waiting-rooms.

On the second floor—members' changing rooms, common rooms, and a writing room; and a large committee room which can also be used as a council diningroom.

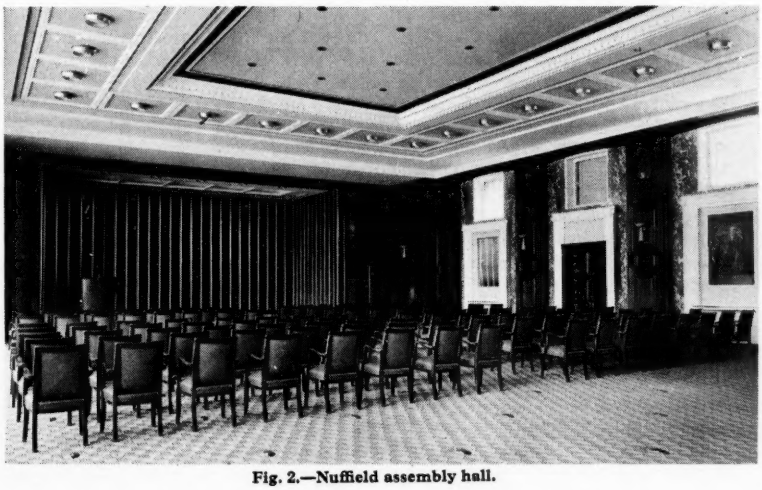

Fig. 2.—Nuffield assembly hall.

1. See *Lancet*, 1957, ii, 945.

On the third floor—the president's flat, and a flat for caretakers.

The basements provide storage space. The building is heated throughout by oil-fired automatic boilers which supply warmth through concealed ceiling panels.

Finance

The cost of the new building—about £400,000—has been met by the members and fellows themselves, and by the public and industry. In particular Lord Nuffield and the Provincial Hospitals Trust have contributed £125,000; the Wellcome Trust has given £30,000; and the Simon Marks Trust £10,000.

Architects.—Louis de Soissons, Peacock, Hodges, Robertson of London.

Builders.—J. Gerrard & Sons Ltd. of Manchester.

Public Health

"EPIDEMIC" NEPHRITIS IN NORTH ESSEX

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IN March, 1959, the head teacher of a village primary school informed me that 3 of her pupils, 2 of whom were brothers, had recently developed acute nephritis. The parents of all the children were considerably alarmed. The epidemic nature of acute nephritis, due to a type 12 *Streptococcus pyogenes*, has been pointed out (George et al. 1958, Pleydell and Hall-Turner 1958), and it was decided to investigate this outbreak.

INVESTIGATION

Nose and throat swabs were obtained from all the children, the teachers, and the domestic staff. Bottles for urine specimens were distributed together with an explanatory letter to the parents, and the specimens were collected on the following day. *Strep. pyogenes* was isolated from 11 children, and the only 4 which were typed were found to be type 12. 1 case of acute nephritis was discovered, and the urine of 8 other children was found to contain red blood-cells. None of the adults were carriers of *Strep. pyogenes* and none showed any urinary abnormalities. All the children who were carriers were excluded from school and given a seven-day course of oral penicillin. Subsequent swabs showed them to be free from infection. None of the patients with acute nephritis had any history of sore throats.

As a check on the spread of infection outside the school, all the older children from the village who attended the secondary school (school I) four miles away were examined, and 2 of them were found to be carrying *Strep. pyogenes* type 12. Nose and throat swabs were also taken from children attending another secondary school (school II) seven miles away, and none of the children were found to be carrying *Strep. pyogenes*.

No further cases of nephritis were notified in the district until six months later when 1 was reported from a boy's private school eight miles from the school originally affected. He was a day-boy and had attended school for only one day after the summer holiday when he developed acute nephritis. Fourteen days previously he had had an acute pharyngitis which had been treated with a course of sulphonamides. Nose and throat swabs were taken from all the boys in his class and his contacts at home. 5 of the boys in his class were found to be carrying *Strep. pyogenes*, of which there were 2 type 12, 2 type 22, and 1 type 4. His mother and a friend of his were found to be carrying *Strep. pyogenes* type 12. All the carriers were given a week's course of oral penicillin.

Six weeks later 1 of the 2 boys who had been carriers of a type 12 *Strep. pyogenes* developed acute nephritis. After his first course of penicillin he had remained well for three weeks, after which he had developed an acute pharyngitis which was treated with oral penicillin. Three weeks later acute nephritis developed. All the boys in the school, the staff, and the children of the staff who were in contact with the boys had nose and throat swabs taken and the urine investigated. 19 were found to be carrying *Strep. pyogenes*, which in 18 was type 12. Of these 18, 16 were in close contact as they were boarders, and only 1 day-boy was found to be a carrier. The urines of 4 boys contained red blood-cells, and the urines of 4 others contained casts. The urines of 3 adults contained red blood-cells. All the carriers were given a week's course of oral penicillin.

Data on the outbreaks are summarised in the accompanying table. The outbreaks in the two schools showed one important difference. In the first school no history of a preliminary sore throat was elicited, while in the second school there was a sharp outbreak of sore throats among the boarders in the latter part of November and the early part of December. This difference may have been due to the closer contact in a boarding-school and a consequent increase in the load of infection which produced clinical symptoms. 1 boy developed acute nephritis despite two separate courses of oral penicillin, to which the organism was reported to be sensitive. This suggests an undue sensitivity to the organism rather than insufficient treatment. The exclusion of carriers and the treatment with penicillin proved to be effective in preventing the spread of infection in the first school, but in the second school it was not effective. This may have been due to the failure to investigate the whole school on the first occasion, with the consequent continued presence

DATA ON OUTBREAKS OF ACUTE NEPHRITIS

Time	School	No. investigated	Carrying *Strep. pyogenes*	Carrying *Strep. pyogenes* type 12	With acute nephritis	Urine contained:	
						Red blood-cells	Casts
February, 1959	*Village school*	84	11	4 (only 4 typed)	4	8	0
	Secondary school I ..	37	2	2	..	Not examined	
	Secondary school II ..	31	0	0	..	Not examined	
October, 1959	*Boys' school*	23	5	2	1	Not examined	
	Home contacts	4	2	2	0	..	..
December, 1959	*Boys' school:*						
	Boarders	71	16	15	1	4	3
	Day-boys	27	1	1	..	0	1
	Contacts:						
	Other children ..	4	2	2	..	0	1
	Adults	19	0	0	..	3	0
	Totals	300	39	28	6	15	5

of a carrier, or it may have been due to the introduction of the causal organism at a later date.

SUMMARY

277 people were investigated (23 of them twice) after detection of 6 cases of nephritis. 28 of the contacts were found to be carrying *Streptococcus pyogenes* type 12. 20 children were found to have symptomless urinary abnormalities, which suggests that the spread of infection was or had been more widespread than the carrier-rate indicated. Oral administration of penicillin to carriers in these semi-closed communities apparently helped to reduce the spread of infection.

I wish to thank all the general practitioners for their assistance in investigating this outbreak, and Dr. J. D. Kershaw for reading the draft of this paper. I should like to acknowledge the assistance I received from the article by George et al. (1958) in formulating the method of investigation.

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Infectious Diseases in England and Wales

Disease	Week ended June			
	4	11	18	25
Diphtheria	1	3	1	3
Dysentery	1236	757	965	800
Encephalitis:				
Infective	4	2	2	2
Postinfectious	..	3	6	1
Food-poisoning	200	344	468	265
Measles, excluding rubella	2488	2478	2936	2465
Meningococcal infection	22	15	17	18
Ophthalmia neonatorum	26	13	25	15
Paratyphoid fever	8	2	8	5
Pneumonia, primary or influenzal	214	220	211	173
Poliomyelitis:				
Paralytic	5	4	15	7
Non-paralytic	6	..	5	2
Puerperal pyrexia	163	149	173	152
Scarlet fever	547	409	346	365
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	423	383	451	426
Meninges and C.N.S.	8	5	7	5
Other	63	53	58	38
Typhoid fever	3	3	..	2
Whooping-cough	1483	1152	1491	1561

The Widdicombe File

LXII.—MEDICAL ILLUSTRATION

DEAR TOMMY,

I see you're in print again. You'll soon be able to put "&c." after mentioning a couple of papers in your potted pen portrait for the *Medical Directory*. And you have illustrations this time, some of them quite good; but are they really necessary?

I suppose you've fallen for the Chinese cliché about one picture being worth a thousand words. I don't know a word of Chinese, but it must be an extraordinarily obtuse language to deserve this axiom. Yet the compulsion to illustrate has now so gripped English-speaking writers in medicine that when Ian Aird wrote his splendid "bible" on surgery without a single picture he felt bound to explain his eccentricity in the introduction. Do you remember how neatly he put it? "There is no doubt that the commonest type of memory is that which relies on visual impressions, yet too close a dependence on visual memory enchains the intellect; the highest faculty of the intellect and the finest communication is language."

We have all become so accustomed to inept illustrations appearing now and then to interrupt our reading, ever since our first textbooks, that we seldom question why they are there at all. Perhaps it is only to break up pages of print the sight of which would otherwise intimidate us, and the ratio of print to picture is governed by some such formula as that used in deciding how many commercials can be shown per hour on I.T.V. Two postgraduate textbooks I'm reviewing at the moment have good examples of ritual illustration. One is of a naked man suspended in blackness, in an attitude suggestive of Buddha rising from the traditional posture or a mortal man lowering himself into a bath; the caption reads: "Paraplegia in flexion". The other is of a little girl lying on a bed with no clothes on and one knee bent up, and looking like your cousin Mary trying to get to sleep on a hot summer night. The caption explains that she has a right hemiplegia and that the left limbs are constantly affected by choreiform movements—which tells the whole story perfectly adequately in words. You are a Thurber fan and probably know his satire on this kind of illustration in "Is Sex Necessary?" He took up a whole page with a map of the world with a caption which went something like this, "We print here a map of the world. We realise that this does not help much but neither does a cross-section of the female body which is usually reproduced in works of this kind."

Many lecturers suffer from the same obsession. Some of the faculty here have become very selfconscious about their classes since that questionnaire the students got up among themselves and which showed how poorly they viewed most lectures. As a result there is a tendency now to try to obscure the inadequacy of a lecture by the number of slides shown, and the more dramatic the better even if barely relevant. I heard Professor Drummond asking one of his men who was off to give the introductory bugs lecture if he had plenty of slides because that was what they liked. The young fellow looked a bit embarrassed and confessed he hadn't any—he preferred, he said, rather shyly but with conviction, to use the blackboard and build things up gradually. Prof. D. was obviously taken aback by so reactionary an attitude, and in one so young. Now I daresay students do like slides. They give them the chance to come in late and go early, and there is always the chance of a good guffaw if one comes on upside down. I've heard students criticise a lecture as "just a lot of slides" but never heard a lecturer condemned because he didn't show enough.

But you're not writing books or giving lectures yet; you are starting your bibliography. Whilst you will be primarily concerned, I hope, with communicating experience, you won't be unmindful that the way in which you set about this will stand as a testament to your industry, thoroughness, discrimination, and all that. You may even hope that, when your advancement is considered, some at least of your judges will have the curiosity to read at least some of your papers rather than rest content with comparing your total number of papers with the aggregates of your rivals. In any event, better no paper at all than one which will reflect poorly on you; and when you remember that most readers will only get as far as the summary and the pictures you will realise these are just as important as the text and the references on which you lavish care.

Authors of original papers are trying to say something new (even if it is no more than what happened to *their* cases of such and such a condition) and are therefore concerned with convincing readers of the truth of their statements. On the principle that the camera cannot lie photo-

graphs are sometimes invoked to add veracity to the text. One of our neurosurgeons (they still seem obsessed by the need to emphasise that some of their patients recover) ends a paper this way, " The patient is doing well at school and his behaviour is good (fig. 7)." This figure is a passport-type of head-on view, barely showing all of the face of a boy, faintly smiling, which could as well be a vacuously grinning defective as the vigorous normal child it is meant to be. It adds nothing to the text. This is only one type of inappropriate illustration and there are many others. Such as those of apparatus, either set out in a stylised way like a sister-tutor's trolley or scattered casually as in a shop window; these pictures seldom illuminate any detail for anyone unfamiliar with the equipment and are not needed by those who know it already. Their only possible function would be to show how neat or handy some gadget was but the scale which this demands is often left out.

If after all this you insist on illustrating your next paper you will have to face the problem of making your pictures and diagrams say what you want them to. I've shown you how easy it is for plans to miscarry. Many of us are lucky enough to have had departments of medical illustration set up in our hospitals, and they can help a lot not only by doing the actual work for you but by advising on the best type of presentation, on layout, on whether a photograph or a drawing will be best, and so on. However, as they have got over their teething troubles some of these departments have begun to develop tedious habits not unlike those of better-established ancillary departments such as pathology and radiology. The tail begins to wag the dog and you begin to wonder who is supposed to be helping whom. You know what I mean—the path. lab. that won't let you have the heart of the patient whom you've looked after for three years and on whom you only got a P.M. after a long session with the relatives " because the organs now belong to pathology "; and the X-ray department which tells you that, whether your chief is waiting to incise the chest or not, you can't have the films until they've been reported, and reminds you that the films belong to them. The forms which this tendency takes in medical illustration are more subtle but the result is the same in that you lose control over some aspect of your work when all you are seeking is some technical help.

Of course you may have the perfect department in your place, and think that I am simply a poison pen and showing myself as a good example of how hitherto reasonable people become suspicious and even paranoid when they get on the staff. But I fancy you do have problems, because of your last figure. I suppose it's meant to persuade the reader of your honesty when you say the young man was restored to normal health, and you must have been pretty pleased with yourself after the heroics in the night. But only a department of medical photography would have produced *two* views of this lucky patient, one a harshly lit full face showing every adolescent pimple and the other a pure profile. No-one else could have imagined that two views at right angles convey health and happiness better than one natural shot. What was needed here, as in the other instance of the normally behaved boy, was a more distant view of the patient doing something natural—riding a bike, playing tennis, or reading a book. If you wish to illustrate, then you must show visual clues—in these cases those indicating normality.

Whilst on inappropriate clinical photographs of patients, a word about nudity, which photographers love and patients don't. If you don't guard against this, your patient may suffer an indignity which even the nurses on the ward take care not to inflict, and without even the comfort of a nurse or doctor near. Here is a woman stark naked to show wasting of one shoulder-girdle. . . .

To return to your figure, part of the fault was yours, both for accepting such a ridiculous photo and for allowing it to be taken. It's up to you to make clear what you want, though even then it's sometimes hard to get it. Newcomers to this part of Yorkshire encounter this sort of trouble in the shops. Our new administrator from Surrey went to buy stiff collars (he always looks much more professional than the doctors) and was told they were out of date and that it was no use his going on trying to get them, and he came out with soft ones. (I wish we could talk him out of things as easily as that.) He tells me that now, when he is asked in a shop what he wants something for, he says quite nicely, " Let's not bother what it's for; I just want one."

With your illustrators, such an approach should be needed only in the last resort. Most of them appreciate your discussing with them what you want to have done, and they will often come up with good ideas that never occurred to you. But you must have the matter well thought out in your own mind first or you may come away with a white elephant. Al Bronson, the Fulbright man we have here from Kansas, had an experience with our department which highlights the situation, thanks to that engaging candour with which Americans conduct their personal relations.

He wanted to have a histogram showing the proportions of a total series of cases which fell into three or four groups. He drew out what he wanted down to the last detail, but discussed it with the illustrator who was to work on it, accepting some suggestions from him and rejecting others. It seems that in the States the Visual Aids Department provides a service which is paid for by each person using it, out of research grants and the like. As it is a business transaction the customer says what he wants and is prepared to pay for, knowing that some types of production are more expensive than others, and his is the last word. So Al was a bit taken aback to find his diagram appreciably altered when he went for the prints for publication. When he protested the technician told him that Mr. Wigglesworth had passed them. To which Al replied that they would be appearing under *his* name and not that of Mr. Wigglesworth, and he wasn't having such a diagram as this in a paper of his. This was the cue for the technicians to try to confuse him with jargon and gobbledegook, but they had met their match. Al was a teacher in California where a course in audiovisual aids is part of teacher training, and he knew all the words and a few more too. When he came to criticise the layout he was told it had to be that way to fit the format of a lantern-slide, and that when a figure was composed both for a slide and for publication the slide took precedence. This was too much for Al. " Godammit. Don't you guys realise that a slide is on the screen for only 30 seconds, and half the folks are asleep? But a published illustration is there for all time—for my seniors, my peers, my students, and even my children to see. It's easy enough to get into print, but you can't ever get out." This brought Wigglesworth on the scene, and he tried to do a Khrushchev on him; but it didn't come off.

But enough of our private wars. You do see the lesson though, don't you? These departments have standards of their own and are striving towards a perfect production from an artistic angle as the orthopædic surgeons once

used to aim for perfect anatomical reduction of fractures. Just as the orthopods have had to learn that it is function which matters, these illustrators have to realise that the most beautiful photograph is useless if it is not apposite.

So stay in control of your illustrations; and when you've got what you want make sure you label them properly for the Editor, including a sign to show which way up they go. Illustrations are not always sent with galley proofs, and you might get a nasty shock like Sir Daniel whose masterly review of acute pancreatitis for the Year Book was marred by two X-rays of consummate quality but printed upside down.

Your affectionate uncle,

EDWARD G.

PS. You'd better not let this letter drop out of your pocket in M.I. I still rely a lot on Wigglesworth's help to make my papers intelligible, and I wouldn't like anything to get back to him at their regional meeting which suggested that I didn't appreciate him; for I do.

Congresses

INTERNATIONAL SOCIETY OF GEOGRAPHICAL PATHOLOGY

Eclampsia and Pre-eclampsia

THE Society's seventh international conference, under the presidency of Prof. J. H. DIBLE, was devoted to eclampsia and pre-eclampsia in pregnancy and was held in London on June 28–30.

Geographical Variations in Incidence

Dr. T. F. CORKILL (Wellington, New Zealand) described the decline in the incidence of eclampsia from 3 per 1000 births in 1940 to 0·8 per 1000 at present. There has also been a considerable reduction in case-mortality, and he suggested that improved preventive measures and treatment were responsible. Dr. L. RAURAMO (Turku, Finland) described a similar decline in Finland since 1927, which he attributed to improved obstetric care. Prof. PÉTUR JAKOBSSON (Reykjavik) said that the incidence was similar to that in Finland. Prof. A. BRZEZINSKI (Jerusalem) described considerable variations among the four main ethnic groups in Israel, the lowest rate being among Afro-Asian immigrants, despite fairly uniform standards of obstetric care with 96% of all births in hospital. Prof. M. MAGARA (Tokyo) said that there had been a definite increase in incidence over the past ten years, mainly in the eastern humid part of Japan where living standards were highest. Dr. J. L. MASTBOOM (The Hague) described the decline in eclampsia during the starvation period at the end of the war. There was a subsequent slight rise and the incidence is now stationary at 1 per 1000 births.

Dr. J. B. LAWSON (Ibadan) emphasised the difficulties of obtaining reliable figures for incidence in underdeveloped countries. He had the impression that the incidence in Nigeria was low, with an overall case-mortality of only 7% despite very primitive conditions in many cases. Nigerian women seemed to have a lower basal blood-pressure than Europeans, and to develop eclampsia very rapidly during labour. A blood-pressure standard of 140 systolic and 90 diastolic was unrealistic in Nigeria, as women often had fits at levels lower than this.

Prof. CORALIE RENDLE-SHORT (Kampala) gave an incidence of about 2 per 1000 births among the Bantu, despite very little antenatal care. She also confirmed the development of eclampsia very suddenly in labour, often at a relatively low blood-pressure. Dr. B. v. GAVALLÉR (Caracas) described a gradual decline of eclampsia among the very poor in the past ten years, with a present incidence of 1·8 per 1000 births. Dr. H. G. DIXON (Jamaica) found an overall incidence of 3 per 1000 births. The highest incidence was in unbooked multipara from rural communities. Dr. T. P. MAGEE (Trinidad) found that the incidence of eclampsia in Port of Spain was four times higher in East Indian women than in Negro women. There was no difference in antenatal care, childbearing age, and parity between these two groups, but wide differences in dietary habits. Dr. IAN MACGILLIVRAY (Aberdeen) gave the results of a recent survey in fifteen hospitals in the United Kingdom. Large apparent differences in the incidence of pre-eclampsia in adjacent hospitals were probably due to differences in the criteria for diagnosis and selection of cases. The overall incidence of eclampsia was 1·5 per 1000 births. Prof. C. B. F. DAAMEN (Rotterdam) summarised the declining incidence in most parts of the world, and suggested that maternal and perinatal mortality might be better yardsticks for comparisons.

Dr. RICHARD DOLL (London) discussed the reasons for the more than one hundredfold variations in the incidence of eclampsia in different parts of the world. In the recent survey (1958–59) the incidence of a blood-pressure higher than 140 systolic and 90 diastolic among 7344 booked uncomplicated primigravidæ under 30 was greater than 20%. The large differences in the incidence of pre-eclampsia in different parts of the world were probably accounted for by national differences in mean basal blood-pressure. The response of blood-pressure to pregnancy also varied from country to country and did not seem to be directly related to the diet.

Prof. J. C. MCCLURE BROWNE (London) discussed the clinical aspects of the same series. The average blood-pressure at twenty weeks was 124/73. Increases of 60 systolic or 50 diastolic were accompanied by significant rises in perinatal mortality. Perinatal mortality was also increased when the systolic blood-pressure was significantly lower than average. The presence of albuminuria also increased perinatal mortality, but œdema did not. When the mother's age was greater than 30 and the initial diastolic pressure higher than 90 diastolic, then perinatal mortality was increased fivefold. He concluded that any woman with a blood-pressure higher than average in pregnancy should be treated with suspicion.

Mr. G. W. THEOBALD (Bradford) emphasised the importance of the stage of gestation in relation to a rise in blood-pressure, rather than rigid numerical criteria for diagnosis. Prof. L. M. HELLMAN (New York) emphasised the importance of distinguishing between pre-eclampsia and essential hypertension, and suggested that comparisons be confined to primigravidæ under 30.

Dr. KATHARINA DALTON (London) compared the manifestations of pre-eclampsia to the syndrome of premenstrual tension and claimed that treatment of women with certain symptoms early in pregnancy with progesterone reduced the subsequent incidence of pre-eclampsia. Mr. JOHN SOPHIAN (Worthing) identified the underlying renal ischæmia as the cause of the hypertension and suggested that local variations in the amount of salt in the diet might be important. Prof. M. A. VAN B. BASTIAANSE (Amsterdam) suggested that maternal mortality was higher when pre-eclampsia was superimposed on essential hypertension, than in pre-eclampsia by itself.

Summing up, Prof. Sir DUGALD BAIRD (Aberdeen) discussed the importance of agreed criteria for diagnosis. Dietary factors had a considerable influence on the incidence of eclampsia and there were also considerable variations from one race to another which could not be explained by diet.

Pathological Changes in Mother and Child

Dr. A. D. T. GOVAN (Glasgow) described the postmortem findings in 116 fatal cases of eclampsia. A quarter showed evidence of chronic pyelonephritis. He also described in detail the lesions in brain, liver, and kidney, and pointed to their basic similarity. He considered that a vascular reaction, with exudation of plasma constituents through the vessel wall, was

responsible and that hypertension was the likely cause of this. Dr. GAVALLÉR also thought that the changes in the brain in fatal eclampsia could be accounted for by a vascular lesion. Dr. H. B. GOODALL (Dundee) reported a case of hæmoglobinæmia and hæmoglobinuria in eclampsia, which he suggested might be the result of hæmolysis of extravasated blood in the liver. Prof. F. TAKAKI (for Dr. E. ISHIKAWA) described the light and electron microscope appearance of the glomerulus. He considered that swelling of the capillary endothelia cells was the most important change, but that mesangial elements might also be involved.

Prof. C. L. PIRANI (Chicago) discussed the electron microscope appearances in 60 renal biopsies from women with pre-eclampsia and eclampsia. The light microscope showed swelling of the glomerulus with narrowing of the capillaries and apparent thickening with "fibrillation" of the basement membrane. Electron-microscope studies showed swelling and vacuolation of the endothelial cells of the glomerular capillaries with laminar bodies and osmiophilic granules, so far unidentified, in their cytoplasm. The epithelial cells of the glomerulus were also swollen and vacuolated, but their foot processes were normal. The basement membrane is also normal. This lesion was found only in the capillaries of the glomerulus. An occasional case showed true thickening of the basement membrane, similar to that seen in membranous glomerulonephritis. There seemed to be no correlation with blood-urea, but a good correlation between the severity of the lesions and the rise in blood-uric-acid. Lesions in the glomerulus were not found in stillbirths associated with pre-eclampsia.

Dr. A. E. CLAIREAUX (London) described the postmortem findings in 346 perinatal deaths associated with pre-eclampsia in the past ten years at Queen Charlotte's Hospital. The overall perinatal mortality was 10·4%. The pathological findings were those attributable to anoxia and prematurity. Dr. Claireaux also gave some preliminary findings of the Birthday Trust perinatal mortality survey which showed that the percentage incidence of pathological findings for south-east England were identical with his hospital series.

Dr. DIXON described the changes in maternal vessels in 200 biopsies taken from the placental bed at cæsarean section. Cases of essential hypertension showed the usual changes of hyalinised arterioles with intimal and medial thickening of small arteries. Cases of pre-eclampsia and eclampsia showed changes very similar to those of malignant hypertension. Dr. Dixon suggested that fibrinoid necrosis was followed by lipophage infiltration, to give the picture previously described as "atherosis".

Prof. EDITH POTTER (Chicago), summing up, said that the pathological manifestations of pre-eclampsia and eclampsia could largely be accounted for by lesions of blood-vessels. The results were reduction in placental blood-flow, with increased perinatal mortality, and focal lesions in brain and liver. The lesion in the glomerulus, however, was found in no other condition, and allowed one to make the diagnosis from the biopsy alone. All workers agreed that this "endotheliosis" was a swelling of the endothelial cells and was completely reversible, but the pathogenesis of the lesion remains unknown.

Clinico-pathological Studies

Prof. LEON CHESLEY (New York) discussed the renal handling of salt and water in pre-eclampsia. Women with pre-eclampsia showed an inability to concentrate sodium in the urine after a large intravenous injection of NaCl and a reduced ability to excrete the load in 24 hours, compared with normal pregnant women. This, together with the reduction in glomerular filtration, might account for salt retention in pre-eclampsia. Dr. MACGILLIVRAY described measurements of total body-water and exchangeable sodium. He found that total body-water was increased in pre-eclampsia, more than could be accounted for by fœtus, placenta, liquor, and increase in plasma volume and breasts. The total exchangeable sodium was the same as in normal pregnant women.

Dr. D. A. DAVEY (London) measured total exchangeable sodium in 103 unselected primigravidæ at 16, 26, 36, and 38 weeks' gestation. 11 of these women developed pre-eclampsia, mostly about 34 weeks. Normal women showed a slight fall in exchangeable sodium per kg. body-weight from 16 to 36 weeks and a slight rise after this. Cases of essential hypertension and women who later developed hypertension only showed the same pattern. Patients who later developed hypertension with albuminuria, however, showed a rise in exchangeable sodium per kg. body-weight between 16 and 26 weeks and a fall after that. It was therefore possible to predict the development of pre-eclampsia in the early stages of pregnancy. Mr. M. MAHRAN (Edinburgh) measured the daily turnover in body-water and found it reduced in pre-eclampsia. This abnormality was also present before hypertension developed.

Dr. A. KLOPPER (Aberdeen) gave the results of urinary œstriol determinations using an improved method. There was considerable day-to-day variation, which could be reduced by taking the average of two consecutive days; output tended to be low in pre-eclampsia and very low in cases of intrauterine death, but results were not reliable. Serial determinations were more helpful, but even these showed wide fluctuations. Dr. M. J. R. DAWKINS (London) reported the results of serum-isocitric-dehydrogenase determinations in the last trimester of pregnancy. Transient elevations, probably due to placental infarction, were associated with sudden rises in diastolic pressure in women with severe pre-eclampsia. Dr. EDDA HANINGTON (London) was unable to confirm the previously reported preponderance of blood-group O in pre-eclampsia in a series of 10,000 primigravidæ with pre-eclampsia. The distribution of blood groups was the same as in normal controls. Professor CHESLEY described a highly significant increase in the incidence of eclampsia and pre-eclampsia in the sisters and daughters of women with eclampsia.

Dr. H. HOSEMAN (Göttingen) reported the results of a 20-year follow-up, mostly by questionnaire, in 171 women with pre-eclampsia. He found a mortality of 7·4% and a high incidence of chronic renal disease and hypertension in the survivors. Dr. H. B. GOODALL (Dundee) discussed the considerable local variations in the incidence of megaloblastic anæmia of pregnancy in the United Kingdom and described the value of examining the buffy coat for erythrophagocytosis and primitive cells in making the diagnosis. Many cases of megaloblastic anæmia have hypertension and albuminuria which disappear after treatment with folic acid. Prof. M. MAGARA (Tokyo) described the preparation of a polypeptide from the placenta which caused contraction of smooth muscle and elevation of cat blood-pressure. A similar substance had been found in the urine of women with pre-eclampsia.

Mr. H. B. PARRY (Oxford) described the syndrome of "toxæmia of pregnancy" in the sheep. There were focal neurological signs, hypoglycæmia, ketosis, and depletion of liver glycogen with a great increase in liver fat. Severe cases ended in coma and death, and there was a high perinatal mortality. There was no hypertension but a very significant reduction in renal blood-flow. The disease developed in the last month of pregnancy, and was commoner in sheep which were overweight. It could be largely prevented by rigid dietary control.

Prof. R. J. KELLAR (Edinburgh) said it was clear that isolated studies on salt and water metabolism gave very confusing results. The abnormalities in salt and water metabolism early in pregnancy in women who later develop pre-eclampsia might explain these discrepancies, especially the disagreements on total exchangeable sodium. He agreed that urinary œstriol determinations were disappointing, and found that urinary pregnanediol determinations were of more value in the practical management of pre-eclampsia, especially when the fœtus appeared to be growing normally. He also reviewed some of the enzymes present in large amounts in the placenta and decidua and their possible role in relation to pre-eclampsia.

In England Now

A Running Commentary by Peripatetic Correspondents

IT is the age of the gimmick, I thought sadly, as I left our annual meeting. Even our own profession, hitherto considered immune, seems to have been cross-infected. Dr. A.'s slides, for instance, were magnificent, but they were not without a theatrical flavour. " Dr. A. looking at a mouse " was followed in quick succession by " Dr. A. and his portable mouse-cardiogram ", " Dr. A. pointing to a valve ", " Detail of Dr. A. holding a mouse ", and " Close-up of Dr. A. looking pensively at an illegible graph. "

Dr. B. disdained the use of slides. Instead, with lightning rapidity, he produced from below the rostrum a series of card-board sheets, beautifully lettered and figured, and, between times, jolly cartoons. They say his wife used to teach art. Dr. C., on the other hand, with his opening remark " A funny thing happened to me on the way to this meeting . . . " was not fully appreciated, nor was Dr. D.'s play with his newly acquired monocle, effective though it was in searching for a stray percentage. Dr. E.'s lightning sketches on the blackboard were received rather better, and Dr. F.'s translation of parts of his paper into French for the benefit of the one Gallic member of the audience went down rather well—though, truth to tell, the visitor seemed happier with the main content than with the summaries.

The chief followed his usual habit of dressing inversely to the seriousness of his communication. To a lay audience his black coat and pinstriped trousers are all that sartorial etiquette demands of a senior consultant. The groans that escaped his housemen when he appeared in bow tie, plum waistcoat, heather jacket, tan slacks, and suede shoes were justified by the mental gymnastics needed to follow his exposition of modern immunological trends.

Altogether I think I was the only member who gave a standard traditional lecture, though my hand microphone and portable amplifier did occasion a certain amount of, no doubt jealous, comment.

* * *

She was a little old countrywoman, deaf as they come, who had recently wasted a twenty-seven-mile journey to the nearest hearing-aid clinic. She had arthritis as well. Her visit to me was to obtain treatment for burns on one of her hands. As she left me she said " I could cry sometimes, for joy 'cause people are so good to me." My day was made.

* * *

My peripatetic colleague's cri-de-cœur about the Sunday papers forces me to come to his aid. About six years ago these papers were stuffed, with difficulty, into our narrow letterbox. It took several minutes of manipulation worthy of any obstetrician to deliver the bundle with the minimum of tears. I got rather fed up with suturing the front pages with 'Sellotape' and started to look round for a suitable container. I eventually found one of those mysterious cardboard cylindrical containers with $^1/_2$ in. thick walls which were used by the Services to transport some Special Item. (I have never been able to find out what item.) Anyway, by drilling a hole in one side it hooked on to the knob of our door-knocker and I made a cunning little tray stuck on to the bottom to hold the money. This worked well for a year or two during which time the papers grew in size. I then had to put a rubber buffer on the container because the dwarfs who delivered the Sunday papers scratched the paint on the door putting the paper in. After repainting the door twice I decided the time was ripe to find something else, but as the problem arose only once a week I did nothing until both the papers we take started to issue magazine sections. I have now solved the problem by changing my car and using the front-seat cover from the old car. I cut the cover in half so that the bit which went over the back could be hung upside down on the door-knocker to form a large pouch. I reckon that this will last until the comics arrive. In the meantime I am willing to issue blueprints or paper patterns or give advice on changing the car. The important thing is to choose a car at a time when the old covers are tatty so that one isn't tempted to try and use the old seat covers. I may even go into production of special Sunday-paper pouches: at least I shall be able to claim expenses and with some careful manipulation make it as profitable as a farm which loses money.

* * *

My friend Seamus often says that an English public-school education is like a vaccination—a fine thing once you are over the complications. He admits reluctantly to some Celtic blood, but holds that Ireland (for instance) is finished, mainly as a result of the depredations of foreigners. He is gravely concerned over the decay of moral standards. He finds the high divorce-rate especially disturbing and has been heard to say that when divorce is in the air it's mainly in the heiress. He is hotly anti-Catholic but doesn't want his children—he has none at the moment—brought up any other way because, after all, what other way is there? He sometimes feels that the decline of Ireland is due to drink and he bitterly deplores the poor quality of Irish whiskey in these times. He has travelled widely and considers himself to be a student of civilisation. He says that London would be the finest city in the world, if it weren't for the Irish riff-raff. London has dignity where New York has ambition, romance where Paris has sex, eccentrics where San Francisco has beatniks, sense where Dublin has sensibility. He has scarcely set foot outside London himself for the past twenty years and he believes that England wouldn't be a bad place to live in if it were not for the English.

You may say that Seamus is not too consistent in his attitudes, but once when I accused him of this he replied—" Ach, but a fact is only a fancy that nobody has the heart to change."

* * *

Spain and Portugal may have political similarities, but their attitudes to the visitor are certainly different. I chose to go to the Lisbon congress by train, and I greatly enjoyed the journey. The morning in Paris was brief but fascinating. The eight-course dinner on the Sud Express was delicious. The glimpses of romantic resorts like St. Jean-de-Luz were tantalising. At last, at dusk, we came to the Spanish frontier. Irun: the name itself is like a warning against frivolity. The police were armed. The customs officials were unfriendly: they would speak nothing but Spanish. The sleeper was Victorian and vastly expensive. The carriage doors were locked. In the morning, we were slowly crossing the great bare land of Northern Spain, in which one man and one donkey were to be seen at about five-mile intervals. The last station in Spain, Fuentes de Oñoro (memories of school history-books!) was cold, concreted, bleak, and silent. My passport having been stamped, we rattled through a little defile into a leafy valley and stopped at the first station in Portugal. The people were smiling. A band was playing. The station was painted in bright colours. " Vilar Formoso ", said the notice-boards: " Welcome to Portugal! "

* * *

I always find it difficult to know just how much notice to take of my own children's complaints. We don't like to keep them away from school for every sniffle or tickle in the throat, and yet our pride is hurt every time one comes home saying " Lily took my temperature this morning ". My sympathies are, however, with the school, because when a child is sent home at 10 A.M. with florid measles or chickenpox, the odds are that the father who took it to school was a doctor. And there was another colleague whose daughter fell out of his car as he rounded a sharp right-hand bend on the way to school. She didn't cry much as he dusted her coat and dabbed the grazes. It wasn't until that evening that she mentioned that she could not sit down properly. On inspection it was found that the skin had been removed from a large part of her bottom, and her knickers were firmly stuck on to it until they were soaked off in a warm bath.

* * *

" Any history of mental disturbance in the family? "
" Yes, Auntie went to America in 1930."

Letters to the Editor

ORNITHOSIS AND THE RAILWAY GUARDS

SIR,—As someone interested in the keeping of pigeons, and not unmindful of the importance to public health of ornithosis, I feel that the article in your issue of July 2 makes several statements in respect of racing or homing pigeons on which some comment is necessary.

Firstly, it is extremely important to distinguish between wild pigeons, domestic pigeons of all sorts, and racing pigeons. They have all probably the same clinical liability to ornithosis but epidemically they fall into very different groups, and cases of infection from wild pigeons should not be considered as prima-facie evidence for the same probability of infection from racing pigeons.

To distinguish the groups briefly; domestic pigeons other than racing pigeons are usually ornamental or fancy pigeons; are normally kept in captivity and would normally have low viability. Racing pigeons are usually kept for racing and a very high selection pressure is maintained, not only by racing itself but also by the elimination of those which are unlikely to succeed as racers. This means that in the case of racing pigeons only of these groups, acute or chronic infection by any disease is virtually unknown. The existence of the disease at a subclinical level is arguable, but it could hardly be maintained as a health hazard. There is not, to my knowledge, one case of ornithosis in human beings that has occurred as a result of keeping racing pigeons by normal methods.

The report of Dr. Andrew Semple in Liverpool showed in fact that the so-called homing pigeons were kept in an aviary with three budgerigars and one linnet. They were not free flying nor trained or raced. The examination conducted by the medical officer of health was confined almost entirely to wild pigeons. A limited number of homing pigeons was examined, but no proof of infection was found. Prof. D. L. Hughes, of the department of veterinary pathology, University of Liverpool, stated that there was only evidence which suggested there might have been infection.

I should not like it to be thought that I am trying to minimise the possibility of infection. There is undoubtedly a possibility, but it is of considerable importance to pigeon fanciers throughout the country that this possibility should not be exaggerated, and this may easily happen. For example, the *Times* of March 25, 1959, carried a headline "Pigeons may carry lethal infection", and while technically this is true, it is also misleading when applied indiscriminately to all pigeons. This headline was used in reference to an article in the *Bulletin of the World Health Organisation* by Dr. Meyer, and I have had the pleasure of a long correspondence with him, particularly in reference to the quotation which states, in part, "the world-wide prevalence of isolated infection among pigeon fanciers and operators of pigeon lofts".

Dr. Meyer did not feel that he had been accurately reported by the *Times*, and even his actual statement is couched more in the terms of possibility. Referring to the article in *The Lancet*, it seems extremely strange that a budgerigar was not considered a possible source of infection because "it always looked healthy", but that the pigeons, who must have looked healthy, otherwise they would not have been sent training by the pigeon fanciers, were regarded as automatically suspect.

The impression is also given that railway guards are in physical contact with the birds by releasing them. This is not so, although this is of less importance in a virus infection. On the other hand, it does seem a pity that no-one inquired about the health of the owners of the pigeons, since they must suffer a far greater liability to infection. There are also conveyors whose paid job it is to accompany the birds to races, often remaining in the trains many days, and it would surely have been better to have inquired after the health of these men, before talking of the occupational risk to railway guards without qualifying it by suggesting that it might be only a possible occupational risk.

There are some quarter of a million pigeon fanciers in this country, a large proportion of whom live in rented houses quite often rented from local authorities. It is therefore of considerable importance to the sport that the risks of ornithosis, and in particular its danger to public health, should be regarded in the proper perspective and not be the subject of unsupported generalisation. Indeed, when Dr. Semple had been given more information regarding the sport of pigeon racing and the normal methods of keeping them, he agreed himself "that homing pigeons kept under satisfactory conditions are not likely to infect human beings".

You may be interested to know that in order that more facts may be gained we have advised our readers that if they should suffer from respiratory infection, particularly atypical pneumonia or anything similar which does not respond to treatment, they should make sure that the physician in charge knows that they keep and breed pigeons.

If any of your readers have had any experience of infection resulting from ornithosis which can be shown clearly to have resulted from pigeons, this would make more interesting reading.

W. H. OSMAN.
London, W.C.1. Editor, *The Racing Pigeon*.

HYPERTENSION AND RENAL TUBERCULOSIS

SIR,—As the ætiology of systemic hypertension has once more been discussed in your columns, may I draw attention to the possible, if restricted, role that tuberculosis of the urinary tract may play in this respect—controversial though this be?

In 1956 Mr. Howard G. Hanley and myself observed that among 78 patients with renal tuberculosis who had their blood-pressures recorded by the standard bedside method three or four times weekly and always at rest in bed, there were three below the age of 34 with hypertension. No extrarenal cause for this was found in any of the three.

Patient	*Sex*	*Age (yr.)*	*Mean blood-pressure (mm. Hg)*	*Pyelography*
1	M	18	180/110	Poor dye conc. by lt kidney
2	M	18	220/180	No dye conc. by rt kidney
3	M	33	220/140	No dye conc. by lt kidney

Intravenous pyelography revealed no concentration of dye in two cases and impaired concentration in the third, but this abnormality was found in at least 10 of the remaining cases. Parenchymal or pelvi-ureteric tuberculosis was present in all three.

After nephrectomy, pressures of patient 1 fell within "normal" range; those of patient 2, though much reduced, did not, but papillœdema and renal failure disappeared. Unfortunately, some eighteen months later pressures rose again with evidence of renal failure. The pressures of patient 3 remained unchanged.

Naturally, no conclusions are possible or intended from such tenuous data, but blood-pressures of this order in such young subjects arrest attention and pose the question as to whether tuberculous renal disease may initiate hypertension. Certainly, there are cases in the literature where such a relationship is alleged, but it is fair to say that authentic cases—and there are such (e.g., Pickering and Heptinstall,[1] and Platt and Davson[2])—must be fewer than individual authors have allowed. And, of course, there are those who absolutely deny such a relationship. The major difficulty in the problem is lack of adequate criteria for hypertension in many past papers, especially in regard to blood-pressure and age. Some authors, indeed, have written of "hypertension" with surgical renal disease without even furnishing blood-pressure figures.

For all that, one is left with the impression that renal tuberculosis is probably capable of initiating the hypertensive process in the young (say, in about 1% of cases below the age of 40). The possible mode of action is uncertain, but renal ischæmia due to destruction of kidney parenchyma and/or to hydronephrosis caused by tuberculous disease is, perhaps, the most likely. Hydronephrosis, which Egger[3] demonstrated can give rise to renal ischæmia, sometimes appears responsible for hypertension.

1. Pickering, G. W., Heptinstall, R. H. *Quart. J. Med.* 1953, **46**, 1.
2. Platt, R., Davson, J. *ibid.* 1950, **43**, 33.
3. Egger, K. *Z. urol. Chir. Gynäk.* 1938, **44**, 138.

If this is true, it is also important to know whether there is a risk of ischæmia of the tuberculous kidney being more liable to occur today that in previous years under the influence of antituberculous chemotherapy, due, for example, to more rapid healing and fibrosis of ureteric lesions with resultant hydronephrosis or pyonephrosis. This process may be envisaged as operating only in fairly advanced disease.

While one must agree with Peart [4] that " there is such a wide variety (of renal diseases) that it is pointless to consider all the conditions without seeking the common factor " in hypertension, the careful and critical investigation of the tuberculous kidney as a possible instigator of high blood-pressure, though fraught with difficulties, is still necessary—especially today when treatment of the disease is increasingly conservative. Scrutiny of genetic background, strict criteria for hypertension, pyelography, renal angiography, and minute examination of excised kidneys are among the techniques required.

Cardiff. W. RAYMOND PARKES.

NATURE OF HYPERTENSION

SIR,—Some regard primary (essential) hypertension as a quantitative deviation from the norm, and others look upon it as a specific entity.[5] The evidence presented by both proponents, that blood-pressure is a graded characteristic or that levels assume a bimodal pattern among the relatives of hypertensive propositi, is based principally on the prevalence of blood-pressure levels. I submit that many of these approaches are analogous to learning about the nature of diabetes through population surveys of blood-sugar values or about hyperthyroidism by a series of basal metabolic-rates. If a disorder can be characterised only by physical signs or manifestations, which occur also as a result of physiological variations, then it may be necessary to separate those with inconstant or intermittent fluctuations from those with repetitive or established findings.

A minimum of five blood-pressure recordings were obtained at different times, under casual circumstances in the sitting or standing position, on each of 1000 ambulatory afebrile clinic patients aged 45-50. Patients with proteinuria, anæmia, endocrine disorders, signs of valvular disease, evidence of primary renal disease or a previous cardiovascular accident were eliminated from the series. There were 709 women and 212 Negroes in the group.

42 patients were found to have diastolic blood-pressures which were always 90 mm. Hg or higher. 198 other persons had at least one reading of 90 or above. Recording the first or the highest single casual diastolic pressure, or (when available) the lowest reading after rest, a differentiation into two clearly defined groups was impossible. However, taking the mean of the casually-recorded readings or the lowest casually-recorded value revealed two distinct groups with practically no overlap. In the latter instance, two smooth curves of diastolic blood-pressure (79 mm. Hg$\pm$S.D. 6·2 and 98$\pm$5·4) were obtained. But 2 patients in the " intermittent " group had a mean value of 90 or more.

It is suggested that " resting " or single casual values of blood-pressure may give erroneous impressions concerning the nature, presence, or absence of disease. Repeated casual levels of diastolic blood-pressure, on the other hand, suggest that a fraction of the population has a distinct abnormality.

Columbia University College of Physicians and Surgeons, New York. GEORGE A. PERERA.

4. Peart, W. S. *Brit. med. J.* 1959, ii, 5163.
5. Oldham, P. D., Pickering, G., Fraser Roberts, J. A. *Lancet*, 1960, i, 1085.

THE HARVEST MITE

SIR,—This, like all your leading articles, was a well-written, accurate and informative survey of the subject, even though it brought no relief to the sufferers. As a severe reactor to these pests may I add some personal observations?

The areas of infestation are often small and clearly demarcated; in my own village the area is only about 500 acres including gardens, a market garden, and a number of rough pastures. The local farmers are unable to distinguish any difference between the soil of the affected and unaffected areas nor does the degree of cultivation appear to have any relationship to the mite population.

Twice in the past seven years rabbits have completely disappeared from the area, but this has not affected the problem; nor apparently has a change from cattle grazing to sheep on the pastures concerned.

I would support Dr. Roantree (July 2) in his assertion that many people are not attacked, and if Dr. Mellanby (July 9) wants the evidence I would suggest the simple expedient of coming to an affected area and finding out. In a shooting syndicate of 12 men only 2 are attacked, and this is very approximately the ratio throughout the village amongst the immigrants; I know of no case here in a person born and bred in the area. This may of course be familial or acquired immunity. Examination of the skin of an immune person fails to reveal any naked-eye evidence of bites.

This variation of response or attack is found in animals; I have one cat which scratches itself almost bald during the autumn. Some dogs appear to suffer and length of hair seems unrelated to immunity.

I have found the anti-histamines of no value in treatment and agree completely with Dr. Newsome (July 9). Dimethyl phthallate and benzyl benzoate are ineffective as repellants, the only useful agents being paraffin or powdered sulphur, but these repel my family and friends as well. Complete protective clothing I find the only solution, though this year I am experimenting with fruit-tree grease-bands around the top of wellingtons.

My wife, who is completely immune, finds Dr. Mellanby's suggestion that she must be repulsive beyond his experience insulting but is consoling herself with the thought that men are not mites.

Etchinghill, near Folkestone, Kent. DOUGLAS NELSON.

SIR,—Having read with interest your leading article of June 25 and the letter by Dr. Roantree I think it is an important point to recognise that young children are often severely affected by this mite, and that the application of benzyl benzoate is not always satisfactory in the very young. From experience, I have found that after exposure to this mite in areas where it is prevalent, washing of the limbs and face and body with normal saline will remove the mites before they have penetrated the skin. It might be of interest for your readers to note that this was recommended by Gilbert White in *The Natural History of Selborne*.

Chichester. D. WILSON.

" CUFF " HYPERTENSION

SIR,—I read with interest the letter from Dr. Orma and his colleagues (July 2) in which they state that in Finland no sphygmomanometers are supplied with cuffs which wrap completely round the arm. In this country the smaller cuffs supplied for children at any rate frequently do not fulfil the World Health Organisation recommendation and are too short.

I have found that if a narrow cuff is applied to the *outer* side of the arm the " blood-pressure " may be made to

rise beyond the range of the ordinary clinical manometer.[1] Provided care is taken to ensure that the rubber bag lies over the artery and is snugly fitting, gross errors can usually be avoided. They would not, however, occur at all if the cuffs supplied for use in children were long enough to encircle the arm completely.

Amersham General Hospital, Amersham, Bucks. D. H. GARROW.

REDUCTION OF HÆMOLYSIS DURING PERFUSION BY COLLECTION AND STORAGE OF BLOOD IN PLASTIC BAGS

SIR,—Three years' experience of experimental and clinical perfusion using a pump oxygenator have shown that blood damage expressed in terms of hæmolysis may be reduced to a safe level when excessive pressures and turbulence are avoided and when careful attention is paid to the collection and storage of donor blood.

In recent months plastic bags have been used for the collection and storage of blood, and since their introduction less hæmolysis has occurred during the priming and use of the pump oxygenator for perfusion.

The purpose of this letter is to describe a technique of blood collection which has led to a reduction in hæmolysis.

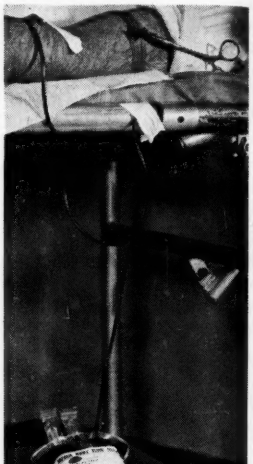
Before June, 1959, blood was collected from donors in the following manner: Bottles siliconed with M.S.1107 and containing 100 ml. of reconstituted plasma with 1500 units of heparin as an anticoagulant. Needles rendered non-wettable with 'Monocote'. Only silicone rubber tubing was used.

Since June, 1959, blood has been collected with disposable plastic taking sets (Fenwall heparin blood pack [2]). Each bag contains heparin sodium 200 *U.S.P.* units in 30 ml. of buffered isotonic sodium chloride and is designed to hold 500 ml. of blood.

In both methods of collection the blood was kept at room temperature for approximately one hour and then in a water-bath at a temperature of 40°C for approximately 30 minutes before priming the pump oxygenator.

Hæmolysis expressed as an increase in plasma-hæmoglobin has been taken as an index of blood damage (see table). Plasma-hæmoglobin was estimated by the method of Fielding and Langley [3] on blood samples drawn from the oxygenator immediately before and at the end of perfusion. All perfusions were carried out using a modified Melrose N.E.P. pump oxygenator.[4]

The plasma-hæmoglobin levels at the end of perfusion do not represent the total hæmolysis, as free hæmoglobin is removed from the bloodstream by the liver and kidneys. It is, however, improbable that the 64% fall in hæmolysis upon the introduction of Fenwall bags should be attributed to improved clearance of hæmoglobin in the cases where the bag was used. Neither can the fall be attributed to any alteration in the manner of preparation and use of the pump oxygenator. The exact reason for the reduction is not known, but it is probable that the following factors contributed, as they are the main differences in the technique of collection:



Blood being collected with a Fenwall blood pack.

(1) The anticoagulant is now contained in a volume of 30 ml. sodium-chloride solution (buffered) instead of 100 ml. reconstituted plasma.

(2) With the Fenwall pack, which contains no air, the blood flows smoothly and gently with no foaming or turbulence, a fault inherent with the bottle technique.

(3) During transportation there is little or no agitation of the contents of the plastic pack.

(4) The Fenwall plastic is chemically inert and contains no silica (or other rare metals).

EFFECT OF PLASTIC BAGS ON HÆMOLYSIS

Case no.	Flow-rate (litres per min.)	Duration (min.)	Plasma-hæmoglobin (mg. per 100 ml.)		Index of hæmolysis
			Before	After	
1	2·04	40	21	102	4·75
2	2·28	29	34	150	10·0
3	3·3	14	53	75	3·04
4	3·24	31	18	61	3·08
5	2·5	185	28	160	1·64
6	3·8	22	52	73	2·02
7	2·6	45	85	135	1·97
8	3·1	19	38	70	4·6
9	3·0	54	46	90	2·3
		Fenwall bags introduced			
10	3·0	38	8	30	1·57
11	3·0	160	24	115	1·35
12	2·3	37	17	43	1·82
13	2·25	18	16	38	3·25
14	2·5	38	17	26	0·79
15	2·75	46	15	23	0·52
16	2·8	26	20	37	1·63
17	3·0	25	22	31	0·91
18	3·0	38	15	21	0·40

The grammes of free hæmoglobin added per 100 litres of blood pumped has been taken as an index of hæmolysis.

For the first nine perfusions blood was collected using siliconed bottles and for the last nine using Fenwall bags. The mean fall in the index of hæmolysis upon the introduction of the bags was 64%.

We wish to thank Mr. G. H. Wooler, Dr. P. G. F. Nixon, and Dr. A. Ambery Smith for their assistance and encouragement. One of us (H. M. S.) was aided by a grant from the Nuffield Foundation.

H. M. SNOW
Technician,
Department of Thoracic Surgery
A. COULSON
Chief Technologist,
Blood Bank.
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AN UNUSUAL FORM OF FAMILIAL OSTEODYSTROPHY

SIR,—On June 4 you published a paper from me in which I suggested that this condition had not been described before. Since then I have received from the Clinique de Génétique Médicale in Paris a reprint of a 1957 paper by Maroteaux, Lamy, and Bernard [1] describing an identical condition under the name of "late spondylo-epiphyseal dysplasia".

In the families studied all the cases occurred in males and the lateral radiograms of the spine show the same "codfish mouth" appearance. It is stated that the condition was first described by Nilsonne [2] in 1927, anteceding Morquio and Brailsford by two years.

I have been able to check three of their major references and although two of the accounts—Nilsonne [2] and Jacobsen [3]—are not entirely convincing there is no doubt that the appearances described by Volhard and Drigalski [4] are the same with similar radiographic changes.

The interesting point that emerges from all these papers is the delineation of a condition characterised by an arrest of

1. Garrow, D. H. *St Geo. Hosp. Gaz.* 1954, **39**, 99.
2. Dudley, H. A. F., Richmond, J., McNair, T. J., Paton, B. C., Cumming, R. A. *Lancet*, 1958, i, 294.
3. Fielding, H. E., Langley, P. E. *Amer. J. clin. Path.* 1958, **30**, 528.
4. Nixon, P. G. F. *Lancet*, 1959, i, 1074.

1. Maroteaux, P., Lamy, M., Bernard, J. *Pr. méd.* 1957, **51**, 1205.
2. Nilsonne, H. *Acta. chir. scand.* 1927, **62**, 550.
3. Jacobsen, A. W. *J. Amer. med. Ass.* 1939, **113**, 121.
4. Volhard, E., Drigalski, W. *Zbl. inn. Med.* 1937, **58**, 243.

development of the spinal column between the ages of ten and fourteen occurring only in the males of certain families and seemingly behaving as a sex-linked recessive. The changes in the spine affect the epiphysis with malformation of the vertebral bodies producing characteristic codfish-mouth appearances.

Buxton. H. STUART BARBER.

ELECTROCARDIOGRAPHY AND HYPERKALÆMIA

SIR,—With reference to the letter of April 16 by Dr. Narasimhan, I should like to point out that there is nothing surprising in finding E.C.G. changes in patients with a plasma-potassium level of 6·5 mEq. per litre, whereas E.C.G. changes are not found in other cases with plasma-potassium as high as 7 mEq. per litre. The serum-potassium level at which electrocardiographic changes take place varies considerably in different patients. The prolongation of QRS complex sometimes precedes the change in T wave and P wave.

Moreover Dr. Narasimhan said nothing about the serum-sodium and serium-calcium levels in his patients. An increase in serum-sodium and serum-calcium can reverse the effect of a raised serum-potassium, and an essentially normal electrocardiogram may be recorded.

Medical College, Pondicherry, India. S. CHANDRASEKARAN.

CARCINOGENICITY OF IRON-DEXTRAN COMPLEX

SIR,—There is an increasing awareness of factors which may be responsible for the development of certain forms of malignant disease. There is also evidence that some common foodstuffs and widely used drugs can, in certain circumstances, induce the formation of tumours in one or more species of laboratory animals. It is against this background that new reports of carcinogenicity must be judged. The most recent of these is the evidence that iron-dextran complex (' Imferon ') is capable of giving rise to sarcomas at the sites of repeated injections of massive doses in rats and mice. This evidence was considered sufficient to warrant a demand [1] for the withdrawal of imferon from any kind of general use in man.

After carefully considering the available data in connection with the carcinogenecity of iron-dextran complex we have concluded that its use in the clinical dosage recommended carries a negligible risk and is probably less hazardous in other respects than intravenous iron preparations and blood-transfusions. In our opinion, provided that the presence of severe iron deficiency has been clearly established and provided oral iron cannot be employed effectively, the injection of iron-dextran complex is fully justified and practitioners in this country and abroad need not be deterred from using the drug.

Rheumatic Diseases Unit, Northern General Hospital, Edinburgh. J. J. R. DUTHIE.
Department of Medicine, University of Edinburgh. R. H. GIRDWOOD.
Department of Pædiatrics and Child Health, Children's Hospital, Birmingham. DOUGLAS HUBBLE.
Department of Materia Medica and Therapeutics, University of Aberdeen. A. G. MACGREGOR.
Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow. E. J. WAYNE.
Department of Pharmacology and General Therapeutics, University of Liverpool. ANDREW WILSON.
Department of Pharmacology and Therapeutics, University of Sheffield. G. M. WILSON.

1. *Brit. med. J.* 1960, **1**, 788.

COST OF BECOMING A DOCTOR

SIR,—Professor Morris (July 2) deplores the tendency for medical students to be drawn substantially from professional and business families and says that if this persists " serious issues must arise ". What are these issues which are presumably to be solved by mass manufacture of silk purses from proletarian ears?

The proprietor of the small sweet and tobacco shop can afford the cost of medical education and may do so as an intelligent act or as a social step, but often " brass " and business are preferred to education.

Education is not a matter of money plus school and university. A family which encourages a child's interest in everything from astronomy to zoology is a favourable home in the scientific sense whatever its social group. Those irresistibly attracted by science should be scientists. Other arrangements may please politicians but are artificial and undesirable. If we can have adequate grants available for all who need and merit them, whatever their social status, then few brains will be lost.

Department of Pathology, Whipps Cross Hospital, London, E.11. C. RAEBURN.

VESICULAR ERUPTION ASSOCIATED WITH GRISEOFULVIN

SIR,—More serious side-effects of griseofulvin than hitherto reported, necessitating cessation of treatment, may be of interest in view of the opposite experience of Dr. Brian Russell and his colleagues, reported in your issue of May 28.

The patient was a married woman of 38 with *Trichophyton rubrum* infection of the toenails and one thumbnail, of 17 years' duration. The deformities were gross and had earlier prevented her, on medical grounds, from going abroad as a missionary. Apart from slight eczema in childhood there was nothing relevant in her past or family history. She was given 1 g. of griseofulvin a day in four divided doses. Only transient headaches, possibly unconnected, occurred until after the 20th day, when an irritating vesicular eruption appeared on the backs of her fingers and hands. In spite of treatment with prednisolone lotion locally, chlorpheniramine maleate (' Piriton ') 24 mg. daily by mouth and 40 mg. daily by intramuscular injection, and later prednisolone 15 mg. daily by mouth, the eruption continued to spread. 25 days after treatment began there was gross swelling of her fingers and hands so that they were unusable, and both upper limbs were covered with an erythematous vesicular rash. The condition of the lower limbs was similar, but later and less gross. There was also an urticarial eruption on the nose, periorbital tissues, and ear lobes, with a vesicular rash behind the ears spreading down to and involving the neck.

At thist time her condition was so severe that she could not look after her family, and griseofulvin was stopped. After 36 hours the eruption began to subside and the irritation became less. The skin returned to normal 12 days after stopping griseofulvin. An intradermal test with griseofulvin carried out at this point was strongly positive, but a patch test was negative. The blood-picture showed hæmoglobin 95% (Haldane), white cells 5800 per c.mm., polymorphs 34%, eosinophils 10%, basophils 1%, lymphocytes 52%, monocytes 3%.

Most side-effects of griseofulvin so far reported have been transient and mild. Beare and MacKenzie [1] point out low toxicity and found only nausea in 2 out of 50 children. Headache and malaise in several patients were reported by Barlow et al.[2] and 5 out of 34 patients treated with 2 g. daily developed an erythematous rash, disappearing in 4 patients when the drug was discontinued

1. Beare, M., MacKenzie, D. *Brit. med. J.* 1959, ii, 1137.
2. Barlowe, A. J. E., Chattaway, F. W., Hargreaves, G. K., la Touche, C. J., *ibid.* p. 1141.

(the 5th had fever, dizziness, general malaise, and vomiting). Dr. Russell and his colleagues reported headache during treatment and other minor symptoms attributable to the drug, but they state that these side-effects were as common among controls as among those receiving griseofulvin.

Although the drug could not be given to our patient for the long period normally accepted as necessary, it is nevertheless considered probable by some workers [3] that the laying down of a bed of healthy nail during the three weeks she had treatment may presage cure.

The sensitivity tests to griseofulvin were kindly carried out by Dr. A. Scott.

Dorking, Surrey. PATRICIA GOODE.

PAY INCREASE TO MEDICAL SUPERINTENDENTS

SIR,—In his letter of July 9, Dr. Gore states that the revocation of Statutory Instrument 1948, no. 419, will mean that the responsibility of a medical superintendent of a mental hospital will be neither greater nor less than that of his fellow consultants.

We know that the Minister has decided that the appointment of a superintendent shall no longer be compulsory, but it would be strange if he decided that when one is appointed he should not be permitted to superintend.

Many consultants still think that a special-purpose hospital needs a doctor in day-to-day control, and would welcome the appointment of one of their colleagues to take this responsibility as an alternative to their being under the tutelage of a lay administrator.

Whether the appointment should be on a temporary or permanent basis is a matter of opinion and does not affect the main issue—nor does the proposed extra £250.

Northgate and District Hospital,
Morpeth, Northumberland. C. GUY MILLMAN.

ADRENALECTOMY AND HYPOPHYSECTOMY

SIR,—I should like to comment on Mr. Macbeth's letter of June 25 advocating the transnasal approach to the pituitary fossa for the ablation of the normal pituitary gland. Neurological surgeons have, of course, been aware of this possibility since the first decade of the century and 167 of Cushing's 260 operations for decompression of pituitary tumours were done by the transseptal transsphenoidal route.[4] The method was largely superseded by the transfrontal approach about 1928 but was revived by otolaryngologists, notably Hirsch, in the 1930s.

Actuated by the same sentiments as those expressed by Mr. Macbeth—that the operation would be less disturbing, the convalescence smoother, and the hospital stay shorter—we operated on a group of patients in 1957 by the transsphenoidal route. We quickly became aware of the difference between the safe operation for the removal of a pituitary tumour in which the subarachnoid spaces in the area have been previously obliterated by tumour growth and the operation for complete removal of a normal pituitary gland which results in a free communication being established between the cerebrospinal-fluid pathways round the pituitary stalk and the nasal sinuses. All our patients developed cerebrospinal-fluid rhinorrhœa, two of them a very troublesome recurring meningitis, and all of them were dead within five months of the operation. This might have been predicted from the high complication-rate following mechanical insertion of yttrium rods through the sinuses reported by Forrest,[5] somewhat reduced by using screws to seal the hole in the anterior wall of the sella.

We abandoned the method and would advise otolaryngologists, who might be influenced by Mr. Macbeth's letter to explore the method, that unless they can suture the dural defect in the floor of the pituitary fossa necessarily created, their operation will be followed by cerebrospinal-fluid rhinorrhœa in a large number of cases unless it is incomplete and does not reach the pituitary stalk. It is tempting to think that such a dural defect can be made good by packing it with muscle, fibrin, or some form of plastic material, but they and their patients will find to their sorrow, as we did, that this is not so.

Department of Neurological Surgery,
Royal Victoria Hospital,
Belfast. ALEX R. TAYLOR.

GUIDE FOR PUDENDAL NERVE BLOCK

SIR,—I should like to confirm the merits of the guide for pudendal nerve block described by Dr. Eaton and Dr. Flanagan (June 25). It has been found most useful at Perivale Maternity Hospital and elsewhere during the past eighteen months. A transvaginal pudendal block is more quickly and accurately performed using this device and new house-surgeons learn the technique easily.

The guide is now being made in this country by Messrs. Down Bros. and Mayer & Phelps, Mitcham, Surrey. The gauges described are American gauges, and the equivalent English ones are no. 17 and no. 20 respectively.

Perivale Maternity Hospital,
Greenford, Middlesex. A. M. DICKINS.

THE CAUSE OF ŒDEMA IN "COR PULMONALE"

SIR,—May we comment on the suggestion of Dr. Campbell and Dr. Short (May 28) that œdema in cor pulmonale may be due to the increased bicarbonate reabsorption which is known to occur in the presence of a raised arterial carbon-dioxide tension?

They have perhaps not considered that increased bicarbonate reabsorption need not be accompanied by increased sodium reabsorption, since bicarbonate ions may instead be substituted for chloride ions in the reabsorbate. That such substitution does occur during the compensation of respiratory acidosis is clear from the plasma-electrolyte pattern in which, characteristically, the bicarbonate concentration is high, chloride low, and sodium normal. This elevation of plasma-bicarbonate at the expense of chloride will not cause expansion of the extracellular fluid with œdema formation; for this to occur, not only bicarbonate reabsorption, but also sodium reabsorption, must increase.

Evidence concerning the effect of a high pCO_2 on sodium reabsorption in otherwise normal humans is very difficult to obtain, because experimental subjects cannot tolerate severe or prolonged hypercapnœa. Such human experiments as have been performed have shown neither a significant rise in sodium reabsorption nor expansion of the extracellular fluid, but they involved relatively brief and modest elevations of carbon-dioxide tension.[1–3] Recent studies [4,5] in rats exposed to carbon-dioxide concentrations between 8 and 15% for periods of up to eleven days have also shown no significant changes in urinary sodium or in sodium balance. It may be argued, however, that the rat is not a suitable experimental model. Information concerning the response in the dog is perhaps more pertinent, since in many respects the renal function of this animal more closely resembles that of man.

In the paper on chronic respiratory acidosis in dogs by Sullivan and Dorman,[6] no data on sodium balance or sodium excretion during chronic hypercapnœa were reported. However, we have recently completed balance studies in five dogs exposed to carbon-dioxide concentrations of 9 to 13% for periods of up to eight days. The sodium excretion was some-

3. Scott, A. Personal communication, 1960.
4. Cushing, H. *J. Amer. med. Ass.* 1914, **63**, 1515.
5. Forrest, A. P. M., et al. *Brit. J. Surg.* 1959, **47**, 61.

1. Longson, D., Mills, J. N. *J. Physiol.* 1953, **122**, 81.
2. Barbour, A., Bull, G. M., Evans, B. M., Hugh Jones, N. C., Logothetopoulos, J. *Clin. Sci.* 1953, **12**, 1.
3. Barker, E. S., Singer, R. B., Elkinton, J. R., Clark, J. K. *J. clin. Invest.* 1957, **36**, 515.
4. Levitin, H., Branscome, W., Epstein, F. H. *ibid.* 1958, **37**, 1667.
5. Carter, N. W., Seldin, D. W., Teng, H. C. *ibid.* 1959, **38**, 949.
6. Sullivan, W. J., Dorman, P. J. *ibid.* 1955, **34**, 268.

what increased during the first few days of hypercapnœa in every dog, and though it later returned to the control level in all but one, it did not fall significantly below that level. None of the dogs gained weight. In a further group of seven dogs studied on a low-sodium diet, there was a smaller but still significant urinary sodium loss in the early days of hypercapnœa. All the 12 dogs had an increased bicarbonate reabsorption and an increased chloride excretion. Thus, although it is clear that during chronic respiratory acidosis the *proportion* of filtered sodium reabsorbed with bicarbonate must have increased, this increase was offset by a decrease in the proportion reabsorbed with chloride, so that no net sodium retention resulted.

We feel that the evidence we have quoted makes it unlikely that hypercapnœa per se is the cause of the œdema in cor pulmonale.

A. POLAK
GORDON HAYNIE
Tufts University School of Medicine, Boston, Mass. WILLIAM B. SCHWARTZ.

CONFIRMATORY MEDICAL CERTIFICATE BEFORE CREMATION

SIR,—No two crematoria put quite the same wording on their forms, with or without statutory authority. Two variants known to me throw light on Dr. Hinden's remaining difficulties.

One quotes in a marginal note Home Office advice to the effect that form C in hospitals should be signed by a doctor "not in charge of the case" (underlined). Clearly "the relevant registrar" is inappropriate. Another subdivides form C, question 3, thus:

3(a) Have you made a post-mortem examination?
(b) Have you had a post-mortem report, and if so from whom?

actually going beyond the charge suggested in Dr. Hinden's original letter (June 18) and showing that at least one medical referee does not share Dr. Hinden's doubts about reports at second hand. After all, most patients are satisfactorily cremated without postmortem at all!

Fees are not governed by statute. The appropriation by hospital authorities, under a forced interpretation of the Terms of Service, of any fees paid for form B is a well-known grievance; but "unfair" division of fees resulting from strict limitation of the right to sign form C can be dealt with by mutual arrangement within the hospital.

Summerfield Hospital, Birmingham. ROBERT J. HETHERINGTON.

EXPIRED-AIR RESUSCITATION

SIR,—The letter of June 4 from Dr. Dobkin shows that one important point in my earlier letter was not appreciated. When a new procedure is put forward or an old one revived, it must be examined fully before being generally adopted. Where the medical profession is concerned this is important but for the lay public it is paramount, because they do not understand frequent changes of this type and not all of them learn to be efficient at the method quickly. For this reason I stressed the need for study of emphysematous patients and operators, as well as the difficulty in getting an airtight seal in the edentulous, before official recognition was made.

But it is also essential for the procedure to be studied from the point of view of the instructor. It is known, for example, how difficult it is to persuade the medical student learning to administer anæsthetics to keep the angle of the jaw forward in the supine patient and thus maintain an adequate airway; but how much more difficult will it be for the layman? Ruben et al.[1] have examined this and say that although it was difficult to remember to maintain an airway and not easy to perform, they felt that the procedure was effective. The ability of students and laboratory staff to learn the method does not necessarily bear relation to the ease with which the "man-in-the-street" can learn it.

Perhaps the adoption of expired-air resuscitation in Sweden this year will provide results and stimulate further work, and so remove remaining obstacles to its general acceptance.

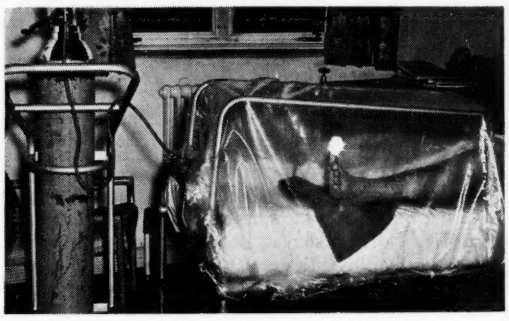
University of Bristol. R. ST. J. BUXTON.

1. Ruben, A., Elam, J. O., Ruben, H. *Lancet*, 1959, ii, 69.

A SIMPLE MEANS OF DRYING BURNS

SIR,—In 1956 an account was published[1] of the exposure treatment of burns as carried out in Baghdad. The beneficial results of this were attributed to the high temperature and low humidity of the atmosphere during the greater part of the year. Whether the heat or the dryness plays the greater part will probably be determined in the experimental unit recently established by Prof. Charles Wells with the help of Mr. J. H. Johnston at the Alder Hey Children's Hospital, Liverpool. In the interim such facilities are not generally available to most other workers, who complain that burns exposed to the English climate fail to dry in less than forty-eight hours. This is the period when infection or bacterial contamination is likely to become firmly established.

In the search for an inexpensive and commonplace contrivance the idea of using compressed air for the purpose



was conceived. Compressed air seemed to possess many advantages. It is readily available in portable cylinders holding 1000 c. ft. and at a cost of a few shillings. Moreover the moisture content is negligible—i.e., about one part per million.

In practice the air is delivered through a flow-meter and directed by a rubber tube to the burned surfaces, and where the area to be treated is extensive, wastage is reduced and efficiency increased by enclosing the part in a plastic cage (see figure). The bag is really a sort of cage with both ends incompletely sealed, so the air can readily disperse. For experimental purposes the effectiveness could greatly be enhanced by the use of a Stannard envelope or Bunyan type of bag, which can be readily tailor-made in polyethylene with various built-in conduit tubes; but, as yet, there has been no occasion when this refinement was thought to be obligatory.

In practice it is found that drying of the burned surfaces is completed in the maximum time of four hours; if further oozing occurs later it can be quickly dried. Naturally the air as delivered from a high-pressure cylinder is cooler than that of the atmosphere of the wards; but one of the guesses made in Baghdad was the apparent reduction in severity of the shock with the exposure treatment. Perhaps some degree of hypothermia is also an important factor and further study might ultimately place the relative merits of the heat and dryness of the Baghdad atmosphere in their proper perspective.

This method has been in use in 38 cases over a period of

1. *Lancet*, 1956, ii, 93.

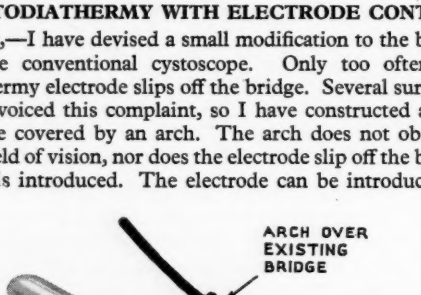
nine months at the Burns Unit, Stockton Children's Hospital, and no case of sepsis has arisen in the first seven days.

We are indebted to the British Oxygen Company, Birtley, for their courtesy and help, and to Sister J. Burns, of Stockton Children's Hospital, for her help in using this method.

JOHN POTTER
W. E. M. WARDILL.
Newcastle-upon-Tyne.

CYSTODIATHERMY WITH ELECTRODE CONTROL

SIR,—I have devised a small modification to the bridge of the conventional cystoscope. Only too often the diathermy electrode slips off the bridge. Several surgeons have voiced this complaint, so I have constructed a new bridge covered by an arch. The arch does not obstruct the field of vision, nor does the electrode slip off the bridge as it is introduced. The electrode can be introduced as



far as the operator wishes, and it will be held quite securely in position. I should be pleased to show this cystoscope to any interested surgeons for their inspection, use and comments.

The modification was carried out by the G.U. Company, and I should like to pay tribute to the excellent way it has been done.

King George V Hospital,
Ilford, Essex. E. TROENSEGAARD HANSEN.

ORAL HYPOGLYCÆMIC AGENTS

SIR,—Your reply to my letter of April 30 commiserates with me for having been so unfortunate as to encounter 6 instances of jaundice due to chlorpropamide. You might be interested to learn that the manufacturers have admitted knowledge of 29 instances of jaundice reported to them directly from the American experience alone. The actual incidence is immaterial since tolbutamide is definitely free from any hepatotoxicity, regardless of the dose, in a vast experience covering over one million patients throughout the world!

Your reference to Heinsen [1] concerns a patient recovering from hepatitis, treated with chlorpropamide without drug impairment of the liver. Surely you are not recommending chlorpropamide as an ideal therapeutic agent for jaundice when it is now generally accepted that chlorpropamide-induced jaundice is an *idiosyncrasy* limited to certain individuals. Unfortunately such idiosyncrasy is currently undetectable before the drug is administered. Popper and Schaffner [2] have stated that "the future is bound to bring more rather than less of drug-induced hepatic injury. The crucial question for patient and physician is the risk involved. The use of a potentially dangerous drug is obviously discouraged if an equally effective, nontoxic alternative is available".

Dr. Oakley and Dr. Jackson [3] request the findings in the cases I cited. Rothfeld et al.[4] reported a near-fatal instance in a patient taking 500 mg. of chlorpropamide daily for 5 days followed by 10 days of 250 mg. daily. Reichel et al.[5] reported an instance of severe protracted (3 months) cholestatic jaundice following the daily administration of 500 mg. of chlorpropamide for 3 weeks. A fatal instance of jaundice, dermatitis, and bloody diarrhœa followed 3 weeks of chlorpropamide in a daily dosage of 250 mg. only (this case is to be published shortly).

It would seem that hepatic damage due to chlorpropamide is not dose-related if the reaction be an idiosyncrasy. If it be dose-related as implied by Dr. Oakley and Dr. Jackson, then certainly the margin of safety for chlorpropamide administration is critically narrow, an item which the current therapeutic recommendations by the manufacturer disregard completely. In fact, the Council on Drugs of the American Medical Association stated,[6] "the influence of lower dosage levels to decrease the incidence of toxic effects remains to be seen".

New York. HENRY DOLGER.

STEROIDS PRECEDING SURGICAL TREATMENT OF ULCERATIVE COLITIS

SIR,—May I congratulate Dr. Ewart and Dr. Lennard-Jones on their paper of July 9? They brought out the point that their findings were substantially in accord with the results of the Gordon Hospital series which I reported last year.[7] I think this agreement needs special emphasis, because the two investigations were carried out independently and each without the knowledge of the other, and the validity of the results is thereby reinforced.

I should like to underline their remarks about the disastrous effects of delaying operation in the seriously ill patient who does not quickly respond to adequate doses of corticosteroids. If these drugs are going to be effective this will usually be apparent within a few days of starting treatment, and one should not wait longer than a week. Even this may be too long, and rapid deterioration (of which colonic distension is the most ominous sign) may demand surgery within a day or so. I believe that delay is the danger, not the steroid, and that failure to recognise this has been the cause of the bad reputation these drugs have acquired among surgeons.

In connection with cortisone "cover" for these operations, your contributors imply that their patients received this for a four-day period, and we would think this was too short; at the Gordon Hospital these cases continue their "cover" for a week with tapering dosage, and some have needed permanent cortisone maintenance if the preoperative period on steroids has been long.

The Gordon Hospital,
London, S.W.1. IAIN MACDOUGALL.

EARLY DIAGNOSIS OF PREGNANCY

SIR,—The findings recorded by Dr. Jaffé (March 19) in 100 consecutive cases of amenorrhœa treated with oral pyridostigmine stimulates immediate interest concerning the method of evaluation employed in his series.

Unfortunately, no criteria other than failure to menstruate has been offered in support of the inclusion of cases in the trial, although later, during the summary, reference is made to 2 patients being menopausal, and 1 girl, aged 21, having infantile uterus at follow-up examination. In this instance it is quite possible that the amenorrhœa was of a primary nature.

Following the administration of 180 mg. pyridostigmine daily for three days, failure to menstruate within a week is stated to indicate a negative result. "Of the patients in whom the test was 'negative' menstruation appeared normal; in no case was there evidence that a pregnancy had been interrupted, though admittedly this cannot be proved."

In the subsequent statistical analysis of results, 100% accuracy is claimed in respect of the negative findings, and 97% for the positive group.

Before the test is accepted as conclusively accurate, one is left wondering to what extent the "vehicle of therapeutic enthusiasm" has been allowed to stray into this uncontrolled series.

Bournemouth. D. READ.

1. Heinsen, H. A. *Ann. N.Y. Acad. Sci.* 1959, **74**, 820.
2. Popper, H., Schaffner, F. *Ann. intern. Med.* 1959, **51**, 1230.
3. *Lancet*, 1960, i, 1077.
4. Rothfeld, E. L., Goldman, J., Goldberg, H. H., Einhorn, S. *J. Amer. med. Ass.* 1960, **172**, 54.
5. Reichel, J., Goldberg, S. B., Ellenberg, M., Schaffner, F. *Amer. J. Med.* 1960, **28**, 654.
6. *J. Amer. med. Ass.* Jan. 2, 1960.
7. MacDougall, I. P. M. *Proc. R. Soc. Med.* 1959, **52**, suppl. p. 9.

AUTOLOGOUS GLIOMA TRANSPLANTATION

SIR,—Unavoidably, the communication by Dr. Bloom and others (July 9) raises the question to what extent such procedures are justified in man. The question was apparent to the authors, who had in mind some addition to our knowledge of tumour immunology; and permission was obtained from the patients concerned, all of them suffering from a rapidly fatal disease.

Clearly, however, justification must depend upon some prospect (even remote) of benefit to the patient, or of some addition to knowledge not otherwise obtainable, the patient then acting as a volunteer. Each year I receive offers from one or two persons, wishing to submit themselves in this capacity. In every case thus far I have felt bound to reply that I do not know of any problem which cannot be solved by other means. This is, of course, merely a personal opinion, and it very well may be that a crucial question will present itself in cancer research in the future, soluble only by experiment in man. In this event, the volunteer will exercise not only a necessary and useful but also indeed a noble function.

It may appear strange to many of your readers that qualms of any kind should be felt by one who has been engaged in animal experimentation over a great many years. I submit there is a distinction, in that we are bound by professional tradition in the human case. However, I believe that in animal experimentation also we should keep matters under continual review. In this country we are fortunate in the control which is exercised by the Home Office, but increasingly I believe that each one of us must impose upon himself the highest standards of responsibility, in which connection we have been greatly assisted by the Universities Federation for Animal Welfare.

I cannot apologise for this letter, and trust it will give no offence to the authors, of whose sincerity no-one can be in any possible doubt. But I am equally certain they have presented a problem which all of us have to face.

Chester Beatty Research Institute,
Institute of Cancer Research,
Royal Cancer Hospital,
London, S.W.3. ALEXANDER HADDOW.

TREATMENT OF CORONARY INSUFFICIENCY WITH VASODILATORS

SIR,—Much has been said in recent years of the merits or otherwise of long-acting coronary vasodilatory drugs and, in spite of the fact that several million tablets are prescribed each month, there still remains a great deal of controversy regarding their precise value. In particular, pentaerythrityl tetranitrate has been the subject of both favourable and unfavourable comment and, whilst I am unwilling to make definite representations in favour of this drug when used alone, I should like to record my experiences with it when used in combination with dihydroxypropyl theophylline and papaverine.

A trial of this preparation ('Corangil'), which has been in progress for one year, involved 54 patients, all suffering from typical angina of effort and all having E.C.G. changes of either old coronary infarction or ischæmic cardiac disease. 18 had suffered from one or more coronary infarction. Of these 54 patients, 36 were greatly improved and 10 improved, being judged to be "greatly improved" when only occasional attacks occurred and "improved" when the frequency of the attacks was lessened and the severity of the pain diminished. It was noted in particular that when the 18 patients in the improved or no-response groups were later given corangil together with nialamide ('Niamid') 50 mg. three times a day, further improvement was obtained in 10 patients, whilst 8 patients remained unaffected. When psychological factors were present, the results were worse.

These results, in my opinion, suggest that prolonged dilatation of the coronary vessels by means of drugs is feasible and that this combination of medicaments is worthy of further clinical investigation on a larger scale.

Dudley Road Hospital,
Birmingham. R. O. GILLHESPY.

GRAM-NEGATIVE BACTERIÆMIA

SIR,—Mr. Aldridge's erudite contribution last week draws attention to a potentially fatal condition which occurs occasionally after urological procedures and may not be recognised.

The first case I encountered was in New York and the diagnosis was made by a colleague. A blood-culture was taken and massive doses of intravenous chloramphenicol were given (2 g. every 6 hours). The response was dramatic and it was possible to discontinue treatment after 36 hours. Subsequently a positive culture of *Escherichia coli* was obtained.

A similar case was seen in this country 18 months later in a patient with a uretero-vaginal fistula following hysterectomy; a cystoscopy and attempted catheterisation of the right ureter had been undertaken shortly before the onset of symptoms. The same dose of intravenous chloramphenicol was given and a satisfactory response obtained. The antibiotic was discontinued after 24 hours and the blood-culture made before treatment was started subsequently grew *Esch. coli*.

There is a natural reluctance to give such large doses of an antibiotic even though the duration of administration is short. The response was so dramatic in the first instance that it seemed justifiable to use the same dosage in the second patient who was severely shocked, although I have since wondered whether a smaller dose would have been equally effective. Gram-negative septicæmia is often caused by a relatively resistant strain and it may be necessary to use such a high dose. It would be interesting to know the views of others on this problem.

London, S.W.15. W. F. W. SOUTHWOOD.

MEDICAL ASPECTS OF ROAD SAFETY

SIR,—One cannot help feeling, whatever the individual circumstances of the case reported under it, that the heading "*Drink might make driving better*"—*Doctor's view*[1] is an alarming statement to publicise. The account of the proceedings of the case is short and, as always, one wonders about the context of this statement.

Nevertheless, it is unfortunate that however authoritative a qualification or explanation of such a newspaper heading may be, the damage is already done. However, it raises again certain aspects of the drinking and driving topic and its relation to driving safety as a whole. The current view that oppressive legislation is outmoded because it has proved ineffectual and that the approach should be to awaken public conscience and make reasoned appeals for better driving is akin to preaching to the converted. The public conscience is awake anyway but impotent in the present state of confusion on the subject. The legislation which at present exists is unrealistic, ineffectual, and largely unenforceable anyway—e.g., the 30 m.p.h. speed limit.

It is not our place to comment upon possible improvements in legislation and means of effectively enforcing it. Leading articles and correspondence in the *Daily Telegraph* and else-

1. *Daily Telegraph*, June 15.

where recently cover this and make adequate comment and suggestions. We can and should make clear certain principles which might be expedient in the formulation of it. The psychology of bad driving is a subject which might well be expounded for public consideration. It should be made clear that although the effects of alcohol on driving and accidents is a vastly important subject it is but a part of the whole problem. Unqualified and contradictory accounts of medical views on the topic (for instance of the B.M.A. committee earlier this year and the column I have mentioned) cause dangerous confusion to the layman. The conclusions of the B.M.A. special committee on the relation of alcohol to road accidents is difficult to reconcile with the view represented in the newspaper article cited. Neither would clarification have been helped if he had also seen a television programme last year in which drivers apparently performed tests of skill and judgment better after alcohol than before it. Explanations were offered at the time, but the confusion presumably remains undispelled.

While it is laudable to advocate better roads and eradication of black spots we must surely assist the laymen to realise that an expectation of an appreciable reduction in the accident-rate if and when these objectives are obtained is complete fantasy.

Efficient and safe driving is inevitably a matter of continued and consistent individual judgment. To say this is a matter of conscience is trite, but that same judgment is both necessary in relation to the taking of alcohol before driving and is clouded by its effects. Those with good insight on this matter will be less affected by it but their attempts at compensation may well interfere with their normal powers of judgment and control. That the liability to repeated accident varies according to certain personality characteristics has been shown. The assessment of these characteristics by introspection is least likely to succeed where it is most needed in relation to both drinking and driving. The effects of even small (socially normal and acceptable) amounts of alcohol will be greatest in those who provide, when their blood-alcohol is nil, the greatest menace to road safety. These may be termed the aggressive psychopath type of driver.

The ætiology of this syndrome may be constitutional or conditioned by psychic or other stress and acted out on the roads. In this connection it is salutary to note how often the reasonable and considerate man when transferred from his armchair to the driving seat will be activated into alarming demonstrations of feats of driving "skills". The motorcar provides effective opportunities for compensating inferiority feelings, venting hidden aggression, and allowing ego-ideals to attain reality.

The potentiating effects of alcohol in these release phenomena greatly outweighs, by and large, insightful attempts at counteraction which in this group are minimal or lacking entirely.

However, personality characteristics with or without alcohol and alcohol on its own are but some of the causes of inefficient and unsafe driving. Stress, anxiety, physical illness, fatigue, are just as worthy of consideration.

One would agree that alcohol in regulated doses for anxiety and stress may well produce a safer all-round performance, but its indiscriminate advocacy in this connection is unthinkable. Therapeutic administration of sedatives would be preferable, but some other means of transport ideal.

This is not to suggest that normal anxiety is not a component and necessary part of safe driving and a protective mechanism in itself.

As one's decision to drive and method of doing so is a matter of individual judgment legislation must be directed towards encouraging this. An integral part of this encouragement must be of an inhibitory kind.

Deterrents must be realistic and effective and must be readily applicable to those who require them and unhindering to those who do not. The threat of insecurity is the most potent psychological weapon here and the threat of losing licence and therefore possibly employment the effective deterrent. More ready disqualification for irresponsible driving could produce this effect. As the retired chief-constable points out in his letter to the *Daily Telegraph* (June 15) it would not necessarily lead to more prosecutions. The presence or suspected proximity of a police patrol car is a most effective means of ensuring exemplary driving standards. He quotes his own experience when driving in a patrol car compared with those as an ordinary driver.

The myth propounded by the driver who boasts his ability to drive faster than what would be generally accepted and pleads greater safety on account of his quick reaction times is exploded by Dr. Norman [2] who points out that drivers aged 18–25 who have shorter reaction times and better results on psychokinetic tests generally experience more accidents than middle-aged drivers.

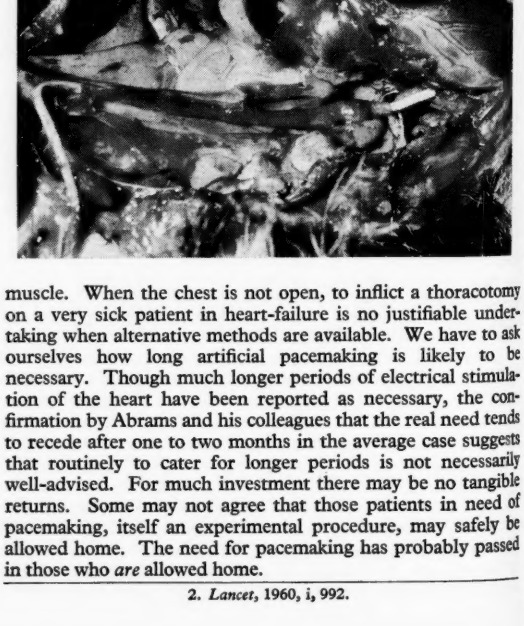
Accidents will only be reduced if we concentrate upon effective methods of deterring those who cause most of them. Application of psychological principles of established validity in the formulation of deterrents is surely the most promising line of approach. A reasoned exposition of established facts would also help to retain the borderline defaulter below the danger threshold. It would help him to improve his ability for fruitful introspection and reflection upon his driving habits and technique and their unconscious or unintentional modification by factors over which he could, in fact, exercise control.

Carlton Hayes Hospital,
Leicestershire. J. F. CLEOBURY.

MANAGEMENT OF HEART-BLOCK

SIR,—The interesting paper by Mr. Abrams and his colleagues (June 25) indirectly touches upon the surgical indications for one or another pacemaking technique. Unfortunately, apart from dimensions in one plane, no technical data of their coils are provided.

Confronted with an open chest, as during an operation for ventricular septal defect, the surgeon's most straightforward procedure is to insert an electrode directly into the heart



muscle. When the chest is not open, to inflict a thoracotomy on a very sick patient in heart-failure is no justifiable undertaking when alternative methods are available. We have to ask ourselves how long artificial pacemaking is likely to be necessary. Though much longer periods of electrical stimulation of the heart have been reported as necessary, the confirmation by Abrams and his colleagues that the real need tends to recede after one to two months in the average case suggests that routinely to cater for longer periods is not necessarily well-advised. For much investment there may be no tangible returns. Some may not agree that those patients in need of pacemaking, itself an experimental procedure, may safely be allowed home. The need for pacemaking has probably passed in those who *are* allowed home.

2. *Lancet*, 1960, i, 992.

From the point of view of simplicity the method of Furman and Robinson,[1] referred to by the authors, has much to recommend it, though difficulty in negotiating the tip of the electrode into the large veins or into the right ventricle may make the external jugular approach [2] easier. A soft catheter electrode strengthened for its passage into the ventricle by a stainless-steel wire trocar should cause little difficulty, particularly under fluoroscopic control. The risk of cardiac perforation mentioned by the authors diminishes to vanishing point when soft braided wire [3] is used. Thrombosis, the other risk, is to some extent inevitable, though its importance can be exaggerated. In the accompanying photograph, taken from a dog, which had *not* been anticoagulated and which had an indwelling catheter electrode for 10 days prior to sacrifice, the thrombus forms a smooth sheath around the electrode down to the level of the tricuspid valve. We have learnt from experiments lasting two months that, again without anticoagulants, this sheath in the large veins becomes absorbed, but round about this time small vegetations tend to appear on the valve leaflets. We do not know as yet if anticoagulants may or may not prevent these from appearing.

Thoracic Surgical Unit,
Guy's Hospital,
London, S.E.1. F. E. WEALE.

1. Furman, S., Robinson, G. *Surg. Forum*, 1958, **9**, 245.
2. Weale, F. E. *Lancet* 1959, **2**, 73.
3. Nightingale, A., Weale, F. E. *Guy's Hosp. Rep.* 1960 (in the press).

BACK PAIN AND HYPERÆSTHESIA

SIR,—What I particularly liked about Dr. Glover's masterly description of this syndrome was the fact that he avoids the trap of conjuring up some hypothetical pathology and indeed says that "the exact anatomical structure at fault cannot be deduced".

As I see it, Dr. Stoddard's point is that for years osteopaths (equally ignorant of exactly what goes on in the spinal joints) have pointed out that this syndrome exists and is relieved by manipulation.

Dr. Cyriax would have us believe that all is now made clear if we think of an internal derangement of the spinal joint as the cause of the pain. He postulates that because of this the vertebræ become fixed and manipulation unlocks the joint, as can occur in a knee. I wish I could share his confidence that this is what happens.

Lastly, Sir, Still did suggest as long ago as 1874 that something could happen to a spinal joint which would cause pain and that manipulation was capable of relieving this pain. The osteopaths must be forgiven for attaching too much importance to this spinal lesion when they found that by manipulation of the spine they could relieve a pain in the chest which had been diagnosed elsewhere as pleurisy.

London, W.1. W. HARGRAVE-WILSON.

Parliament

Sewage Pollution of Beaches

ON July 7 Mr. MICHAEL STEWART said that reliable reports came from every part of the country of beaches made unfit for decent use by sewage pollution. One reason for the persistence of this nuisance was that there had been paralysis of judgment and action during recent years while a committee of the Public Health Laboratory Service inquired into the health aspects of the matter. The committee was set only one question—namely, was there on present evidence a causal connection between bathing in contaminated sea-water and catching poliomyelitis, typhoid, or other diseases? The report told us that it could not be said that there was such a causal connection. Even that limited conclusion was qualified by the statement that there might be some revolting beaches where one could not give even that exemption from evil effect on health. During their six years, the 18 members of the committee examined about 40 beaches. As far as Mr. Stewart could discover from a study of the report, they did not bathe on any of the beaches. They relied on tests of the sea-water. The committee concluded that the disintegration of masses of human excreta before pushing it into the sea might be "æsthetically desirable". It seemed to Mr. Stewart that decency, cleanliness, or amenity were all more suitable words. Local authorities, he urged, should consider better methods for the treatment and disposal of sewage. The Government should establish a nationally accepted standard for a decent beach, carry out a quick inquiry into methods of treatment of sewage and siting outfalls, and consider the financial aspects of the problem. It was absurd to create a society in which more people could afford to visit the seaside but in which the community was too poor to keep the beaches decent.

Sir KEITH JOSEPH, parliamentary secretary to the Ministry of Housing and Local Government, in his reply stressed that there was no health risk against which the Minister must protect the public. The risk was the purely local one that authorities whose beaches were seriously polluted might cease to attract holidaymakers. Nearly all coastal authorities discharged sewage to the sea. Disposal to the sea, provided that it was efficient, need not cause pollution and was a satisfactory method of treatment. Most coastal authorities did not have pollution. There were some with a degree of pollution and a few, no doubt, with grossly polluted beaches. These could be offensive and it was for the local authority concerned to take action. The knowledge was available to advise them where to place their outfalls. Power to obtain loans was available. Grant for those who could not afford it was available through the rate-deficiency grant system. All that was needed was the willpower.

Mr. ERIC FLETCHER did not agree that the matter was purely one for the local authorities. It was a national matter, and the existence of so many beaches in such a disgusting condition was a strong reflection on the Government. We had lagged a long way behind the proper requirements of sewage disposal generally. During the last generation or so there had been so many new urban developments, such a growth of population in certain areas, so much extension of travel, and the caravan habit, that sewage disposal had not kept pace with other social developments.

Dr. REGINALD BENNETT was unconvinced by the findings of the M.R.C. committee's report. They had carried out their experiments on the salmonella but not on the coli group of bacilli, and had not offered any evidence for their claim that sea-water disinfects. It seemed to him contradictory to condemn a drinking-water supply which had more than 1 coliform bacillus in 100 ml. of water and yet suggest that swimmers could apparently drink gallons "with floating solids in it without risk". He asked the Minister not to stand pat on pseudo-scientific negativism which defined the commonsense of the whole country.

Mr. HENRY BROOKE said that he would like to be known as the "Minister for Clean Beaches". He was glad to say that the state of our beaches was improving, but a few were repellent. We could argue till the cows came home about the precise element of health risk, but nobody in his senses could wish to bathe on them. The Public Health Act, 1936, placed responsibility for effectively dealing with the contents of their sewers squarely on local authorities. That responsibility had always been accepted and large sums had been spent on sewerage, sewage treatment, and sewage disposal by both inland and coastal authorities. There was no evidence of authorities being financially unable to do their duty of cleaning up their beaches. He hoped the debate would influence laggards. Since the end of the war successive Governments had authorised expenditure of about £300 million on sewage-disposal and sewage-treatment work. Hundreds of millions of pounds more certainly needed to be spent, but it could not be done by magic. Strong, continuous pressure was needed, from the Minister, from Parliament, and, above all, from local public opinion. The report by the M.R.C. committee was a

responsible document which could not be ignored. Until another group of doctors had made an equally scientific investigation of the subject, he must accept the findings of that report, but he had not the slightest desire to encourage complacency. At the same time he did not want to exaggerate either the number of beaches that needed treatment or the extent of the health risk.

QUESTION TIME

Implementation of Mental Health Act

Sir HUGH LUCAS-TOOTH asked the Minister on what date the Mental Health Act would be brought into operation.—Mr. WALKER-SMITH replied: Sections 1 and 149 have been operating since Oct. 6, 1959, to the extent necessary to permit informal admission to mental hospitals. I have made an order appointing July 15, 1960, as the date of commencement of other sections, the chief of which are sections 6 to 10 which deal with local-authority services. I intend to bring all the rest of the Act into operation on Nov. 1, 1960, the earliest practicable date.

Mr. KENNETH ROBINSON: While welcoming the fact that the Minister is implementing further parts of the Act during the current week, may I ask what is the delay in implementing the remainder of it?—Mr. WALKER-SMITH: The reasons why I cannot do it before Nov. 1, 1960, for the residual parts of the Act are two. First, because the hospital and local authorities must be given sufficient notice to familiarise themselves with the advice in the circulars, which will be lengthy; second, because certain preparatory action has to be taken by the local authorities. Owing to the fact that local authorities are not very active during August and September, it has been necessary to fix the date for Nov. 1.

Mrs. BESSIE BRADDOCK: Will the Minister make certain that no patient is discharged from hospital until the local authorities have the necessary services to accept them? I am told that in some parts of the country there is already friction between the hospital authorities and the local authorities because the hospital authorities insist on discharging patients without consultation with the local authorities. In view of the very grave difficulties that can arise for individuals who have been in hospital for some time unless there are the proper facilities for the local authorities to accept them, will he make certain that the local authorities and hospital authorities know of his decision and requirements in this matter?—Mr. WALKER-SMITH: It is, of course, vitally important that there should be very close liaison between the hospital authorities and the local health authorities in regard to these matters, and I am sure that the supplementary question will serve to remind them still further of this necessity.

Hospital Building Programmes

Mr. ROBINSON asked the Minister to what extent the hospital capital programmes already announced would be affected by the Government's decision to maintain capital expenditure for the coming year at its current level.—Mr. WALKER-SMITH replied: It is not expected that the hospital capital programme already announced for next year in England and Wales will be affected.

Assistants' Salaries

Mr. L. A. PAVITT asked the Minister of Health what was the rate of increase in the average salaries paid to assistants in general practice following the two interim awards to their principals: if, when he made any retrospective payment to general practitioners in accordance with the recommendations in the Pilkington report, he would take steps to ensure that assistants would receive retrospective increases proportionate to the sums received by their principals.—Mr. WALKER-SMITH replied: The conditions of employment of assistants are a matter for private contract between each principal and assistant and no information is available centrally from which recent average salaries could be calculated. I understand that the representatives of the medical profession have the interests of assistants well in mind. Mr. PAVITT: Is the Minister absolving himself from responsibility by throwing this matter back to the medical profession? Is he aware that local executive councils have an account of the net salaries paid to assistants for superannuation purposes? Cannot he keep himself informed by taking a cross-section or sample of this? Will he use the machinery at his disposal to give justice to these people in view of the fact that back-pay is given to general practitioners at the time when cheques are authorised by the local executive council? Mr. WALKER-SMITH: I am prepared to look into the statistics which the executive councils have to see whether they aid us in this matter, but these arrangements are the subject of private contract. Therefore, it is not for me to lay down precisely what should be done. I am pleased with the assurances given by the chairman of the General Medical Services Committee that the doctors will do the right thing by their assistants. Mr. PAVITT: I thank the Minister for promising to look into this matter. There is a private contract between the principal and assistant, but, at the same time the recommendations of the Pilkington report, if carried out, will mean a great increase in salary for the principal during the time of the contract. Will not the Minister seek to ensure that a proportion of it is passed on to the assistant through the machinery which he has at his disposal? Mr. WALKER-SMITH: The distribution will be agreed with the medical profession, and the medical profession has said that it will do the right thing by its assistants. Part of the Pilkington Committee's recommendations is that this system should continue on the basis of settlement by private agreement between the doctor and the assistant.

Colonial Medical Service

Dr. BARNETT STROSS asked the Secretary of State for the Colonies whether he was aware of the need for the expansion of the Colonial Medical Service, and whether he would take steps to integrate the service with the National Health Service.—Mr. IAIN MACLEOD replied: I am aware of the need for a steady increase in the numbers of doctors available for service in the dependent territories, and my department has had a fair measure of success in recruiting doctors to meet requests made by Governments. The large territories in East Africa are increasingly using local doctors qualified at the medical school of Makerere. Arrangements are already in force for doctors in the National Health Service to serve overseas while preserving their pension rights here, and where home employers are able to keep a post open while a doctor is serving abroad, secondment is arranged. Dr. STROSS: Does not the Minister realise that I have asked for integration because it would make it easier for personnel to go out and do a term of service without losing their chances of promotion at home? Mr. MACLEOD: I do not believe that integration in that sense is possible or practicable, because there are so many employers of doctors here and so many employers of doctors abroad. However, we are in consultation with the British Medical Association and will continue those consultations to ascertain what arrangements we can make on the lines of the comment in my main answer.

Mr. BRIAN HARRISON: Will the Minister make certain that there is an adequate number of non-medical people in the administrative services so that he does not have a farcical situation, such as happened at the hospital in Aden, where the doctors were doing the whole of the administrative work and wasting their special skill? Mr. MACLEOD: Yes, that is certainly important. With regard to doctors, there are 50-odd vacancies, and a number of these, which are for specialist posts, are rather difficult to fill.

Brand Names of Proprietary Drugs

Mr. F. E. NOEL-BAKER asked the Home Secretary what representations he had received from the chairman of the Advertising Inquiry Committee regarding the sale of proprietary drug products whose formulæ had been changed since he introduced his regulations, though the original brand names had been retained and in some cases similar claims continued to be made by the makers.—Mr. DENNIS VOSPER replied: The chairman of this committee asked for comments

on the situation described in the question. The Minister replied that he has no power to control the naming or advertisement of medicinal preparations but that he understands that the Working Party on the Law relating to Medicinal Substances will review statutory restrictions on their advertisement. Mr. NOEL-BAKER: Would it not be a good thing if, arising from the work of this working party, power was taken? Swindles are being perpetrated on the public on a considerable scale. The firm which makes the drug 'Persomnia', which may now not be sold without a prescription, has produced a new formula and is marketing it under the same name. There are other instances. Is it not time to take steps to protect the public from frauds of this kind being perpetrated? Mr. VOSPER: I have seen the advertisement to which the hon. Gentleman refers. There may well be something in what he says. It is not a matter for the Poisons Board, but it may well be within the jurisdiction of the working party to which he has referred.

Obituary

SEYMOUR GILBERT BARLING

C.M.G., M.B.Birm., M.S.Lond., F.R.C.S.

To the many surgeons of this country who saw Seymour Barling at the dinner of the Association of Surgeons in Birmingham three months ago, looking well and vigorous, and happy to be with old friends at the Medical School he had served so well, his death will have come as a surprise. Yet he was in his 80th year, and soon afterwards he fell ill. He died on July 4.

He entered the Birmingham Medical School in 1898, qualifying in 1903, and then held hospital appointments, including one at Great Ormond Street. He was appointed to the staff of the General Hospital, Birmingham, in 1910. For some years he was the assistant of his uncle, Gilbert Barling, whose influence in the Birmingham Medical School and, later, in the University lasted nearly 50 years. Barling was a keen Territorial officer in the R.A.M.C. and served throughout the 1914–18 war, finishing as consulting surgeon B.E.F.

He returned to Birmingham to the senior staff and from then onwards was a leader in teaching, practical surgery, and the policy of the hospital as a teaching institution, this last activity culminating in the planning of the new Queen Elizabeth Hospital and the amalgamation of the staffs of the General Hospital and Queen's Hospital. He was elected professor of surgery in the University and served on both the council and court of examiners of the Royal College of Surgeons of England. He was essentially a general surgeon but with a special interest in thyroid surgery, stomach surgery, and the surgery of infancy. He published a number of papers, and, in collaboration with his life-long friend Leonard Parsons, the well-known book *The Diseases of Infancy and Childhood*.

Soon after his retirement from Birmingham, Professor Barling was appointed the first chairman of the South Worcestershire hospital management committee. Of his work there N. D. writes:

"The change from the somewhat rarefied and academic atmosphere of university and teaching hospital to the more humdrum and workaday problems of an outlying and largely rural group of hospitals was not easy. But with adaptability and tact, Barling quickly gained the respect and confidence of his committee and of the medical staffs, most of whom were general practitioners. Under his energetic chairmanship in this mixed group of fifteen hospitals of all sorts and sizes, some small and redundant units were closed; the large new tuberculosis hospital at St. Wulstan's, Malvern, was opened; a complete integration of Worcester Royal Infirmary and Ronkswood Hospital was initiated; and the modernisation of Powick Mental Hospital began. By the time of his retirement under the age-limit, he could look back on seven years of steady progress, carried through with energy and a minimum of friction. To mark these achievements, a ward at Ronkswood Hospital was named after him. He kept an active interest in the work of the group, and was a coopted member of sub-committees dealing with the mental and tuberculosis hospitals."

Some years before leaving Birmingham Barling had acquired a weekend and holiday retreat at Alfrick on the Herefordshire border—a quiet countryside of little wooded hills, orchards, and hop-yards. Here he spent an active retirement. The fine village hall was largely a result of his practical interest and help in local affairs. He was an enthusiastic and successful gardener, and was especially proud of his woodlands, where he enjoyed forestry work almost up to the last.

In the late summer of 1940 Barling offered the Royal College of Surgeons of England accommodation for its library and other possessions at his country house, and W. R. L. recalls:

"Some hundreds of feet of steel shelving supporting tens of thousands of volumes were set up in the great barns at Alfrick and in the long drawing-room, which Mrs. Barling generously gave up to the purpose. John Hunter's collection of paintings was also housed in Mrs. Barling's charge. Mr. Barling was busily engaged as a consultant under the Emergency Medical Service and had to travel much about the Midlands, but he was usually able to spend his weekends at Alfrick, and as librarian of the college from time to time I enjoyed his hospitality. It was a privilege to come to know this generous, modest man on his own ground. Despite his devotion to his profession and his public duties, in the best tradition of his family, I am sure that he was never happier than when entertaining his friends and colleagues. The parting guest usually received choice fruit from the fine garden which he and Mrs. Barling tended so skilfully. His children, then just of age, were caught up in active war service, and he was naturally both proud and anxious. His daughter has since distinguished herself as an authority in personnel management and welfare, and both his sons have followed him into medicine."

F. A. R. S., to whom we are indebted for much of this memoir, adds the following personal tribute:

"Seymour Barling came of farming stock and his love of country life, pursuits, and skills never waned. Indeed, the broad streak of common sense exhibited in all his hospital activities, both clinical and administrative, as, also, his will to live a well-balanced life, probably stemmed from this contact with the good earth. In his early days assistant surgeons were very much assistants, and it may well have been his own experience that made Barling so sympathetic concerning the young man's lot, insisting that he ought to be given the opportunity and wherewithal to visit centres abroad, and that he should be provided with enough beds to allow him to build up special interests and experience while his mind was fresh and receptive. Barling was always prepared to face changing times, whether it was to accept specialisation, to break with tradition, or to change hospital organisation.

"Seymour Barling was a strong personality, yet had great charm, and there are few who came under his influence who have not cause to be grateful for good teaching, sound and kindly advice, genuine friendship, and a fine example of absolute integrity, consideration for others, fair play to all, and a determination once his own time was up to retire gracefully into the background, leaving a clear field to younger men. To return to his beloved country gave him complete contentment. The simple memorial service on July 10, at St. Mary Magdalene, Alfrick, was attended by some 200 people, a significant tribute to one who had retired fifteen years ago."

HENRY SEAWARD MORLEY

M.D. Lond., F.R.C.P.

Dr. Seaward Morley, senior physician to the Royal West Sussex Hospital, Chichester, and a member of the General Medical Council, died on July 5 while on holiday in Pembrokeshire. He was 63 years of age.

He was the son of Henry Foster Morley, D.SC., and he was educated in London at University College School and University College. During the 1914–18 war he served in the R.F.A. and after demobilisation continued his studies at University College Hospital Medical School, qualifying in 1924. After spending six years in resident appointments at U.C.H. and holding clinical assistantships at Brompton and Great Ormond Street Hospitals, he settled at his family home in Midhurst. Besides his appointments at the Royal West Sussex he joined the staffs of other hospitals in the district, including Graylingwell Hospital and Midhurst Hospital. He was elected F.R.C.P. in 1948. For many years he was associated with the Society of Apothecaries of London, and he served as master in 1953–54. Since 1952 he had sat on the General Medical Council as a Crown representative.

G.S.T. writes:

"Seaward Morley has been a friend of mine for just over a quarter of a century and as the years of our friendship moved on I came to admire him more and more. His knowledge of medicine was of a high standard, and his dedication to his work and patients was meticulous. No trouble was spared for both rich and poor to help them in their afflictions and to restore them to health whenever possible. I served on many committees with him and I was always impressed with his grasp of the subject, his lucidity in explaining his point of view, and his absolute fairness. Having made up his mind on a point he would stick to it, but if after listening to his colleagues he was convinced that their views were better he was great enough to bow to the majority decision and give it his support.

"He entered into all entertainments and pleasures with a zest that was infectious. He was an excellent conversationalist, and the subjects he discussed were many and varied. To some he may have appeared at times dogmatic, but this was not so, and as one came to know him better one was struck by his kindness, his courtesy, his understanding of human nature, and above all his humbleness."

Dr. Morley married in 1934 Alison Kathleen, daughter of the late Major Rowland Hill, and she survives him with two sons.

Appointments

ASTIN, MARY K., M.B. Manc.: assistant M.O., Hayes/Harlington, Ruislip/Northwood, Uxbridge, Yiewsley/West Drayton, Middlesex.

BREWIN, P. H., M.B. Leeds: senior assistant M.O. and school M.O., Cudworth, Darfield, Darton, Dodworth, Royston, Wombwell, and Worsbrough, Yorkshire.

CARR, J. M. B., M.B. Edin.: assistant M.O. and school M.O., Castleford division, Yorkshire.

FINE, SHIRLEY R., M.B. Lpool, D.C.H., D.P.H.: senior assistant M.O., Brentford and Chiswick, Heston and Isleworth, and Southall, Middlesex.

FRY, PETER, M.R.C.S.: assistant psychiatrist (S.H.M.O.), Cefn Coed Hospital, Swansea.

GUNN, HELEN E., M.B. Durh., D.OBST., D.P.H.: M.O., London County Council.

Liverpool Regional Hospital Board:

BOOTH, A. J., M.B. Aberd., F.F.A. R.C.S., D.A.: part-time consultant anæsthetist, North Liverpool group and St. Helens Hospital.

MERRIN, D. H., M.R.C.P.I.: assistant chest physician, Cleaver Hospital.

STEVENSON, A. McG., M.B. Glasg.: senior casualty officer, Bootle Hospital.

Manchester Regional Hospital Board:

ALLEN, W. M. C., M.B. Manc., D.M.R.D.: consultant radiologist, North and Mid-Cheshire group of hospitals.

BASSETT, H. F. M., M.B. Lond., F.R.C.S.: part-time consultant thoracic surgeon, South Manchester and West Manchester groups of hospitals.

HILLMAN, FERDINAND, M.B. Belf., M.R.C.P.I.: consultant pathologist, Wigan and Leigh group of hospitals.

HUTCHINSON, J. R., F R.C.S.E.: consultant traumatic and orthopædic surgeon, Burnley and district group of hospitals.

LONGWORTH-KRAFFT, CATHERINE V., M.B. Durh., D.M.R.D.: consultant radiologist, Bolton and district group of hospitals.

PILKINGTON, T. L., M.R.C.S., D.P.M.: consultant psychiatrist and medical superintendent, Cranage Hall and Mary Dendy Hospitals, Cheshire.

Notes and News

THE CONFERENCE ON GOITRE

THE social events of the Fourth International Goitre Conference held in London last week included receptions by Her Majesty's Government, by the presidents of the Royal College of Physicians and the Royal College of Surgeons, and by the president of the conference, Sir Charles Harington.

Speaking at the conference banquet at the Mansion House on July 7, Sir Charles said that the branch of medicine which 650 men and women from forty countries had met to discuss was a very small one, yet of respectable antiquity—for references to goitre ranged over the centuries. The thyroid gland had a curious fascination because so many sciences were brought in to explain its disorders: indeed every branch of natural science had application to the problem of goitre, which could be considered a microcosm of medical science.

Sir Robert Platt, P.R.C.P., while regretting that nobody can now comprehend the whole of science, saw compensation in the fact that medicine can bring together people in almost every scientific discipline; and this was nowhere more evident than in the study of the thyroid gland. He recalled the days of his training forty years ago when so little was known about its disorders and treatment was "very much pre-Astwood, frightfully pre-Harington, and terribly pre-Pitt-Rivers".

Dr. Howard Mahorner, president of the American Goiter Association, described goitre as "one of the most geographic of diseases". That, in all its forms, it could be prevented was not difficult to see; and the world, now becoming a single neighbourhood, would be a better one without goitre. He hoped that from the conference real advances would come.

Dr. Raymond Greene proposed The Visitors from Overseas, remarking that all wars had been due to meetings of politicians but none to meetings of thyroidologists. Prof. Jean Roche responded to this toast and Sir James Paterson Ross, P.R.C.S., to the toast of The Guests proposed by Dr. A. W. Spence.

DRIP-RATE RECORDING AND CONTROL

IN his description of a simple photoelectric monitor for infusion sets, Danbury [1] mentioned that a drip-counter or a drip-rate recorder could easily be added to the basic instrument. A difficulty with rate-recorders and integrating circuits in general is that a finite time must elapse before a change in rate can be indicated: "you must have something to integrate before you can integrate it". For experiments on the effect of oxytocic drugs on the tone of the uterine muscle, during which it was essential to define the drip-rate continuously over a range of 5 to 80 drops per minute, Melville and Cornwall [2] designed an integrating circuit, accurate to $\pm 10\%$, and without the intolerably long time-constant of a conventional resistance-capacity integrator.

Platinum electrodes sealed into the drip-chamber provide a short-duration pulse for each drop. A capacitor is charged from a constant-voltage source for the period between successive pulses, and the final charge reached in each of these periods is a measure of the drip-rate. The electrodes form part of one arm of a Wheatstone bridge, energised at 6·3 volts, 50 cycles per second, for the sake of safety. The circuit proved completely reliable, but Melville and Cornwall recommend the use of a constant-voltage transformer if the mains regulation is poor.

No form of automatic control by feedback from a rate-sensing circuit was used,[3] as satisfactory results were obtained with a positive-displacement variable-speed pump under manual control.

A more elaborate automatic drip-rate controller was developed by the Swiss Federal Institute of Technology in 1953–54.[4]

Basically the circuit is similar to that of Melville and Cornwall; but it includes a sensitive polarised relay to which is applied a sampled voltage, derived from the capacitor-charging circuit, in the interval between drops. The magnitude of this voltage, compared with a stabilised reference-voltage, determines the direction of movement of the relay armature, which in turn controls the direction of rotation

1. Danbury, R. *Lancet*, 1960, i, 905.
2. Melville, A. W., Cornwall, J. B. *Electronic Engg*, 1958, **30**, 606.
3. Melville, A. W., Cornwall, J. B. *ibid.* 1960, **32**, 311.
4. Muller, M. *ibid.* 1960, **32**, 311.

of a small motor operating a screw clamp on the tubing of the infusion set. The number of drops is registered photoelectrically. The drip-rate can be varied between 6 and 180 per minute, with an accuracy of ±5%, irrespective of change in viscosity, venous pressure, or position of the bottle. The instrument has been used continuously without mechanical trouble for as long as seven days on one patient, and is particularly valuable for the control of low drip-rates.

A LITTLE EXTRA HELP

A LARGE number of those helped by the National Assistance Board are old people. The report [1] for 1959 shows that of 1,766,000 allowances 68% went to people over the minimum pension age, including 976,000 retirement pensioners, 118,000 non-contributory old-age pensioners, and 119,000 old people not receiving either kind of pension. The $^1/_2$ million people under-pension age who were being helped were mainly sick or disabled or widows and other women unable to seek employment because of poor health or domestic ties. An appendix gives information about a group of sick or disabled people, about 128,000 not eligible for sickness or any other National Insurance benefit. Most of them have been disabled since childhood.

About 69% of the allowances were being paid as supplements to National Insurance benefits; 976,000 as supplements to retirement pension, 126,000 to sickness benefit, 2000 to industrial-injury pension or benefit, 58,000 to widows benefit, and 59,000 to unemployment benefit.

The Board is able to pay additional sums towards the cost of special diets needed by invalids, laundry for people unable to do their own, and exceptional needs for fuel. At the end of 1959 these powers were being used in about 850,000 cases, over 48% of the total. The additional sums allowed averaged 7*s.* 5*d.* a week and cost about £16 million a year. The Board also has a regular visiting service and the $6^1/_4$ million visits made in 1959 brought to light "many problems and misfortunes to be resolved with the aid of the other statutory services, the advisory committees, and voluntary organisations." Special attention was given in 1959 to the needs of fatherless families, and extra help was given with additional burdens that come as the children grow up.

1. Cmnd. 1085. H.M. Stationery Office, 1960. 3*s.* 6*d.*

University of Liverpool

On July 2 the following degrees were conferred:

M.D.—Geoffrey Barber-Riley, J. D. Bates, A. E. Goetzee, W. H. Parry, P. H. Wright.

Ch.M.—J. K. McC. Rawlinson, *A. V. Forage.

M.B., Ch.B.—K. F. Edwardson, P. A. Murphy, Ann E. Rogers, Mary B. Wallace, Diana Wardle (with second-class honours); Michael Alltree, Susan Almond, R. D. Atlay, *J. M. Barry, Anne Bayley, L. A. Bergman, R. C. Bland, J. A. Blankson, S. N. Booth, W. J. Boyle, Angela M. S. Brown, P. C. Cann, Avril G. Clarke, Merton Cohen, D. E. Cooksley, Raymond Corcoran, B. J. Crane, Averil O. Dring, G. E. Fawcett, W. J. F. Gollins, G. W. Griffiths, D. V. Hicks, I. W. Hughes, H. D. Kaufman, P. J. Keating, E. B. Krasner, M. J. Lipton, Maureen Macdonald, Judith D. Magden, Peter Mann, J. H. Martindale, D. L. Mathias, C. D. Matthews, T. C. Mayer, G. A. Meadows, Janis Laimonis Mikitis, A. R. Morris, Jean C. Moulds, David Ajuebitsi Ogbe, R. D. L. Parker, Donald Pearson, P. A. Rainford, P. W. R. Smethurst, Vivienne S. Strang, C. H. Taylor-Robinson, J. B. O. Thomas, Angela V. Turner, W. A. Warburton, John Webster, Malcolm Webster.

* In absentia.

University of Durham

On July 1 and 2 the following degrees and diplomas were conferred:

M.D.—Sydney Brandon, F. L. Constable, W. R. Dodds, *Henry Madgwick.

M.B., B.S.— Andreas Badohu, N. R. Batey, Rose M. Bell, M. J. Blaiklock, B. C. Bradley, R. A. L. Brewis, Mary Burdus, G. M. Burke, Jennifer D. Burkett, Merica D. M. Carey, Sylvia Carr, Valerie Clarke, Ruth Cohen, Gillian K. Craven, D. R. Cullen, *J. B. Cunningham, Joan Currah, Gordon Dale, W. N. Eastham, G. H. Eeles, Musallam Seif Elbualy, Valerie H. Feltoe, J. B. Garston, I. D. Gilchrist, R. D. Hall, G. H. de G. Hanson, Carl Harnarayan, *Elizabeth T. Hedley Whyte, Margaret Irvine, E. R. Irving, J. A. Jordan, Abu Backarr Kargbo, *L. M. Kremer, Ivar Laurimaa, Marthe A. Le Dune, Elizabeth A. Letsky, Felix Lustman, †Angela C. McArdle, M. J. McCallum, P. P. Meisner, J. W. Muncaster, Clifford Nelson, Ronald Newman, P. A. Nicholson, Marykutty Pawath, J. H. S. Pimblett, E. G. Robertson, A. I. Simpson, Abayomi Olusola Sobo, Sheila Sproat, Leo Strunin, Iris Swanson, P. J. Tallentire, Joan Taunch, J. P. Todd, Patricia A. M. Tootill, R. E. Walker, D. A. Walton, J. K. Ward, B. E. Welsh, Arthur Westgarth, George E. Whittingham, Audrey Williams.

D.P.H.—A. R. Buchan, John Connolly, Margaret McN. Copland, Mary J. Danskin, John Deegan, G. V. Griffin, Margaret A. Loraine, J. F. Mather, D. I. Robertson, Mark Sackwood, John Sarginson, Mary M. Szekely, Mary D. Taylor.

D.P.M.—Pamela Beamish, Valerie Matthews.

* In absentia.

University of Sheffield

Mr. E. L. Hampson has been appointed to the newly created chair of operative dental surgery and Mr. J. J. Hodson to the newly created chair of dental pathology.

University of Aberdeen

Dr. C. J. H. Mann has been appointed lecturer in public health and social medicine.

On July 7 the following degrees were conferred:

M.D.—Malcolm MacLeod, H. G. Smylie (with honours); Alexander Gatherer, G A. McDonald, Marguerite McD. Pereira, *W. J. S. Still, A. J. Watson (with commendation); C. G. Clark, P. E. G. Mitchell.

Ch.M.—R. A. Stephen.

Ph.D.— Manik Singh.

M.B., Ch.B.—Anne M. Wyllie (with honours); S. D. Preston, A. I. G. Davidson, Joan Lees, G. A. Batson (with commendation); C. C. Adomakoh, Anne B. M. Anderson, J. F. R. Bowie, Joan A. Bremner, Jane I. Bruce, Robert Buchan, Ann P. Carter, J. K. Cheriyan, W. G. B. Clark, T. P. Crosgrove, Erica D. Cundill, Margaret Cunningham, J. G. Donald, R. W. M. Downie, R. W. Duncan, Denis Durno, Johanna E. U. M. Ehrhardt, Evaline A. J. Gammack, A. J. S. Gardiner, T. A. Goodbrand, R. L. Gordon, G. D. Gormley, J. R. Greig, A. S. Hunter, N. R. Johnston, Margaret A. Jones, Shirley Jones, Allison M. Kennedy, B. R. Kennedy, F. H. G. Lakin, R. M. Logan, D. Lowe, Margaret T. McCallion, A. G. Macdonald, Calum Mackay, A. A. W. McKechnie, R. N. Mackie, R. D. M. MacLeod, K. J. MacRitchie, Robert Miller, Alexander Morgan, L. D. Morrison, W. McG. Park, A. F. Pringle, J. B. L. Robb, P. W. Ross, K. A. Smith, J. A. Thom, O. A. Thores, W. R. C. Turner, J. A. Wattie, A. R. White, G. G. Whyte, J. F. Wood.

* In absentia.

University of Glasgow

On July 9 the following degrees were conferred:

M.D.—J. F. Boyd, M. B. L. Craigmyle, Eileen E. Hill, I. M. Macgregor, L. S. Scott (with commendation); J. M. Smith.

Ch.M.—J. R. Kenyon, F. C. Walker (with commendation).

Ph.D.—A. I. Carr, W. A. Crawford.

M.B., Ch.B.—David Johnston (with honours); J. A. Boyle, Elizabeth E. Chatton, Janet P. Finlayson, A. M. Gordon, G. D. Lister (with commendation); Niaz Ahmad, Marilyn G. Alberga, Thomas Alcorn, Eric Anderson, J. F. Anderson, I. J. M. Barretto, Graham Bell, J. W. Black, M. A. Rodin, I. E. Boyd, N. T. Bratten, C. M. Brown, Sheila H. Brown, E. C. Buonaccorsi, D. M. Campbell, R. N. Cannon, I. A. Carter, R. K. Chatfield, Mary L. Cochran, A. N. Conner, M. D. Cosgrove, Isabella G. Crerar, R. B. Cunningham, Mary J. Delaney, J. P. Donachie, F. H. Donald, J. P. Donald, A. J. M. Donnachie, Anna K. Donner, R. N. C. Douglas, Margaret J. P. Duncan, M. S. Duncan, G. McK. Dyer, J. A. N. Emslie, R. R. Ewart, J. H. Ferguson, H. J. Fields, Winifred E. I. Finlay, K. H. Fisher, R. S. Fleming, R. J. F. Foulis, Eileen A. Gallagher, Mary Gallagher, W. J. A. Gibson, I. N. Gilchrist, J. T. Y. Gillies, Sheina E. W. Gillies, A. C. A. Glen, E. S. Glen, R. M. Graham, A. R. G. Handscomb, R. McG. Harden, M. G. Harris, R. T. Harrison I. R. Hart, Ann E. Harvey, Anne L. Herd, W. C. Hetherington, N. S. Hodanu, I. M. D. Jackson, A. L. Johnson, Matthew Johnstone, Desmond Kelly, Sheila M. King, M. G. C. Kinghorn, Moira R. McL. Lang, A. G. Levin, James Lind, A. R. Lorimer, J. R. Lorimer, Anne E. P. Loudon, D. L. MacBeath, Maureen McCann, N. W. McCarry, John McCarthy, Fiona R. Macdonald, Elizabeth F. McDonnell, S. M. McDougall, Jean T. Macfarlane, Ian MacInnes, A. M. Mackay, Agnes F. H. MaKerracher, R. F. MacLachlan, K. T. P. McMillan, William McMurray, H. B. McNamee, A. J. Mack, Maurice Mahoney, Katherine E. Mann, A. J. Martin, H. C. Mason, A. W. F. Miller, James Milligan, Alison E. Mitchell, W. A. Muir, Adell Mulholland, J. T. Murphy, A. S. Murray, J. A. Murray, R. B. Napeir, Ian Nicolson, John O'Neill, E. A. Osborne, Elizabeth G. Pate, A. G. Patrick, Munro Peacock, Phyllis Puckel, M. J. Pullen, Carolyn E. Ritchie, J. G. Rogerson, J. R. Rothnie, R. I. Russell, Jawahar Lal Sagar, I. F. M. Saint-Yves, R. D. F. Scorgie, Adebisi Olatunji Senbanjo, G. M. Smith, A. A. Spence, Isobel A. Stevenson, Thomas Stewart, Rachel A. M. Tait, Lillious McL. Taylor, William D. Taylor, I. E. Thompson, John Thomson, J. P. Vance, B. W. McW. Walker, A. S. Wallace, R. J. Weir, J. D. Welch, Jean R. K. White, Helen McL. Wishart, R. H. Wood, Elizabeth J. W. Wright, J. A. Young, J. R. B. Young, Gholam Hassein Zarghami.

University of St. Andrews

Graduates in medicine and surgery are invited to make application for a combined clinical and medical sciences course to be held in Queen's College, Dundee, and for a course in anatomy and physiology to be held at St. Salvator's College, St. Andrews. Both courses will be held from October, 1960, to March, 1961, and the fee for each will be £36. Applications should reach the dean of the faculty of medicine, at Queen's College, before Sept. 1.

National University of Ireland

Dr. Colman Saunders has been appointed to the professorship of pædiatrics, Dr. Edward O'Doherty to the professorship of otorhinolaryngology, Dr. Francis Lavery to the professorship of ophthalmology, and Dr. John Geraghty to the professorship of radiology, all at University College, Dublin. Mr. Leslie Scher has been appointed to the professorship of dental prosthetics at University College, Cork.

Dr. Andrew Heffernan has been awarded a travelling studentship in medicine, and Dr. K. J. Walshe the degree of M.D. for published work.

Royal College of Surgeons of Edinburgh

On Friday, July 22, at 3.30 P.M. at the college, Nicolson Street, Edinburgh, 8, Mr. R. S. Handley will give a lecture on observations and reflections on breast cancer.

Institute of Diseases of the Chest, London

Clinical demonstrations will be continued at the institute, in the grounds of the Brompton Hospital, Fulham Road, S.W.3, on Fridays at 5 P.M., during August and September.

Society for Endocrinology

On Wednesday, July 27, at 5.15 P.M., at 26, Portland Place, London, W.1, Prof. Bernardo A. Houssay, of Buenos Aires, will give the society's annual lecture. He is to speak on an Argentine trail in hypophyseal research.

Royal Society of Medicine

The following officers have been elected for the session 1960–61:

President, Lord Adrian; immediate past president, Sir Geoffrey Marshall; hon. treasurers, Dr. Basil Kiernander and Air Vice-Marshal Sir Aubrey Rumball; hon. secretaries, Mr. Terence Cawthorne and Prof. R. H. S. Thompson; hon. librarians, Sir John Richardson and Sir Eric Riches hon. editors, Mr. Selwyn Taylor, Dr. R. I. S. Bayliss, and Dr. David Pyke; hon. directors of photography, Mr. Myles Formby and Dr. F. C. Kelly.

London Conference on the Scientific Study of Mental Deficiency

This conference, sponsored by the American Association on Mental Deficiency, the Royal Medico-Psychological Association, the Royal Society of Medicine, and the British Psychological Society, in cooperation with the National Association for Mental Health, will be held from July 24 to 29, at B.M.A. House, Tavistock Square, W.C.1. Further particulars may be had from the conference secretary, 39, Queen Anne Street, W.1.

Sir Henry Wellcome Travelling Fellowships

The Wellcome Trustees are providing £60,000 over five years to enable the Medical Research Council to award five travelling fellowships annually of approximately the same status as the Rockefeller medical fellowships and open to workers of similar academic seniority and distinction. The awards will be tenable in any country and for research in any field of medical science, but applications from workers in physiology, biochemistry, pharmacology, and tropical medicine may receive some preference since the Trust has a special interest in these subjects. The fellowships will be formally advertised later in the year.

Experimental Training Course for Nurses

The General Nursing Council for Scotland has approved an experimental scheme of training proposed by the nursing studies unit of the University of Edinburgh. The course, which will begin this coming October, is planned to integrate the preparation for an arts or science degree, with that of the professional nurse. The main hospitals concerned in the scheme will be the Royal Infirmary and the Western General Hospital. The General Nursing Council will exempt students undertaking this course from their preliminary examination.

Conditions of entry will be the same as those for any prospective university student. Students will be accepted after four weeks of planned observation and preliminary experience in a selected hospital. Exemption may be granted if the candidate has previous experience of hospital work. Students will be registered for an arts or science degree and their course will be planned by the director of nursing studies with the directors of studies in the faculties of arts and science. During the first three years while they are taking their degree their course will include both the theory and practice of nursing and they will complete their professional training in the two years after graduation. A wide range of practical experience will be provided in general medicine and surgery, and in the specialties including psychiatric nursing, pædiatrics, obstetrics, and public health.

For the first year, only prospective arts students can be accepted. Applications should be made without delay to the director of studies, University of Edinburgh, 19, Chalmers Street, Edinburgh.

In Memory of W. E. Gallie

Prof. C. F. W. Illingworth has been appointed the first McLauchlin Gallie visiting professor of the Royal College of Physicians and Surgeons of Canada. The professorship has been set up through the generosity of Mr. R. S. McLauchlin, a Toronto business man, in memory of the late W. E. Gallie.

British Association of Urological Surgeons

The following have been elected officers for 1960–61:

President, Mr. David Band; immediate past president, Mr. Arthur Jacobs; vice-president, Prof. L. N. Pyrah; hon. treasurer, Mr. R. A. Mogg; hon. secretary, Mr. D. Innes Williams; and hon. editorial secretary, Mr. N. M. Matheson.

British Academy of Forensic Sciences

The first scientific and general meeting of this academy will be held at the London Hospital Medical College, Turner Street, E.1, on July 22 and 23. The subjects chosen for discussion are education and training, research and investigation, and evidence and witnesses. Further particulars may be had from the secretary, 37, Welbeck Street, W.1.

Accident Management and General Practice

A symposium on this subject, organised by the British Orthopædic Association, the College of General Practitioners, and the Institute of Accident Surgery, will be held at the Medical School of the University of Birmingham on Sept. 24 and 25. Further particulars may be had from Dr. C. M. Green, 8, Albert Road, Harborne, Birmingham, 17.

Great Issues of Conscience in Modern Medicine

A public convocation on this subject will be held at Dartmouth Medical School, Hanover, New Hampshire, U.S.A., from Sept. 8 to 10 under the chairmanship of Dr. René Dubos. Those taking part will include Mr. Aldous Huxley, Sir Charles Snow, Sir George Pickering, Dr. Warren Weaver, Dr. George Kistiakowsky, Dr. Walsh McDermott, Dr. Brock Chisholm, Dr. Ralph Gerard, Dr. Wilder Penfield, and Dr. Sandor Rado.

International Congress on Clinical Chemistry

This congress, organised by the Association of Clinical Biochemists, will be held in the University of Edinburgh from Aug. 14 to 19, under the presidency of Sir Rudolph Peters. The programme will include symposia on plasma-protein turnover in disease, mechanisms of urine production, congenital abnormalities of metabolism, and clinical enzymology. Further particulars may be had from the secretary of the congress, Dr. S. C. Frazer, Royal Infirmary, Edinburgh, 3.

Anglo-American Medical Society

This society has been founded in Cambridge to promote "social and professional liaison between the American doctors in East Anglia and their British colleagues, and to examine more closely attitudes, values and customs as they apply to medicine in both countries". At the first meeting on Wednesday, Sept. 7, there will be a discussion on "the normal pregnancy on both sides of the Atlantic". Further particulars may be had from Mr. A. J. Eden, Cedar Cottage, March Road, Wimblington, Cambs.

Surgeon Captain J. A. Shepherd, R.N.R., has been appointed an honorary surgeon to the Queen in succession to Surgeon Captain K. W. Martin, R.N.R.

Dr. J. P. Quilliam has been appointed a member of the General Optical Council.

On Monday, July 18, at 5.15 P.M., at the Royal Free Hospital, Gray's Inn Road, London, W.C.1, Sir Macfarlane Burnet will speak on auto-immune disease.

Dr. Naguib Mahfouz, emeritus professor of obstetrics in the University of Cairo, has been awarded the State prize for 1960 and gold medal by the United Arab Republic.

CORRIGENDUM: *Lumbar Intradiscal Pressure.*—In this annotation (July 2, p. 30) the last sentence of the first paragraph should have read: "According to Nachemson, about 20% of the weight in the spine is carried through the posterior bony elements."